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Review article

Current understanding of fear learning and memory in humans and animal models and the value of a linguistic approach for analyzing fear learning and memory in humans

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Abbreviations: ACC, anterior cingulate cortex; AChE, acetylcholinesterase; AET, autobiographic episodic training; AMPAR, AMPA receptor; AMT, Autobiographical Memory Test; apoE, apolipoprotein E; apoE2, E2; apoE3, E3; apoE4, E4; BDNF, brain-derived neurotrophic factor; CAPS, Clinician Administered PTSD Scale; CAVE, computer automatic virtual environment; CB1, type 1 cannabinoid receptors; CBD, cannabidiol; CBM, Cognitive Bias Modification; COMET, Competitive Memory Training; CR, conditioned fear response; CRH, corticotropin-releasing hormone; CS, conditioned stimulus; CSF, cerebrospinal fluid; DCS, D-cycloserine; DLPFC, dorsal lateral prefrontal cortex; DMN, default mode network; fMRI, functional magnetic resonance imaging; HMD, head mounted display; HPA, hypothalamic-pituitary-adrenal; Ig, immunoglobulin; l, long; LC, locus coeruleus; LPFC, lateral prefrontal cortex; LTP, long-term potentiation; MDD, major depressive disorder; MEST, Memory Specificity Training; miR, microRNA; miRNA, microRNAs; MPFC, medial prefrontal cortex; NE, norepinephrine; NMDA, N-methyl-D-aspartate; OCD, obsessive compulsive disorder; OFC, orbital frontal cortex; OGM, overgeneral autobiographical memory; PAS, pregnanolone sulfate; PE, Prolonged Exposure Therapy; PEA, palmitoylethanolamide; PFC, prefrontal cortex; PPAR, peroxisome proliferator-activated receptor; PSA, polysialylation; PTSD, posttraumatic stress disorder; s, short; SBSS, selective brain steroidogenic stimulant; SCEPT, Sentence Completion for Events of the Past Test; SNP, single nucleotide polymorphism; SSRI, selective serotonin reuptake inhibitor; TEMPau, Test Episodique de Memoire du Passe autobiographique; THC, Δ9-tetrahydrocannibinol; TSPO, translocator protein; US, unconditioned stimulus; VLPFC, ventral lateral prefrontal cortex; VMPFC, ventral medial prefrontal cortex; VR, virtual reality; VRET, Virtual Reality Exposure Therapy

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ABSTRACT

Fear is an emotion that serves as a driving factor in how organisms move through the world. In this review, we discuss the current understandings of the subjective experience of fear and the related biological processes involved in fear learning and memory. We first provide an overview of fear learning and memory in humans and animal models, encompassing the neurocircuitry and molecular mechanisms, the influence of genetic and environmental factors, and how fear learning paradigms have contributed to treatments for fear-related disorders, such as posttraumatic stress disorder. Current treatments as well as novel strategies, such as targeting the perisynaptic environment and use of virtual reality, are addressed. We review research on the subjective experience of fear and the role of autobiographical memory in fear-related disorders. We also discuss the gaps in our understanding of fear learning and memory, and the degree of consensus in the field. Lastly, the development of linguistic tools for assessments and treatment of fear learning and memory disorders is discussed.

1. Background/introduction

This review is being undertaken as part of the 'The Human Affectome Project', an initiative organized in 2016 by a non-profit organization called Neuroqualia. To launch the Human Affectome Project, a workshop was organized in Halifax, Nova Scotia, on August 4 and 5, 2016. The project aims to produce a series of overarching reviews that can summarize much of what is currently known about affective neuroscience while simultaneously exploring the language that we use to convey feelings and emotions. The goal of this project was to address two related issues: (1) to develop a comprehensive and robust functional model for emotions and feelings that can serve as a common focal point for research in the field and to avoid inconsistent constructs (Izard, 2007); and (2) to support the neurophysiological and anatomical substrates in the brain corresponding to emotions (Panksepp, 2007) rather than emotions being natural kinds (Orteny and Turner, 1990).

The project is comprised of twelve teams that are organized into a taskforce that is focused on the development of a comprehensive and integrated model of affect that can serve as a common focal point for affective research in the future. To that end, our team was specifically tasked to review the neuroscience research related to anxiety and fear and the language that people use to express feelings that relate to anxiety and fear. We were further asked to consider whether or not the feelings that people convey in language might inform the way we approach neuroscience research on these topics. We were also asked to identify the relationships that exist between anxiety and fear and the other areas of affective research within this special issue (*i.e.*, Physiological, Social, the Self, Anticipatory, Actions, Attention, Motivation, Anger, Sadness, Happiness, and Hedonics) and to summarize future research needs.

The current review first provides an overview of fear learning and memory in humans and animal models, including the neurocircuitry and mechanisms involved, the role of genetic and environmental factors, the contribution of fear learning paradigms for treatments of fear learning and memory disorders, as well as a discussion on the degree of consensus and gaps of knowledge in the area of fear learning and memory. In addition, the mechanisms of action of existing treatments for posttraumatic stress disorder (PTSD) and development of novel therapeutic strategies for PTSD, including those targeting the presynaptic environment involved in fear learning and memory and those involving virtual reality (VR) are discussed. Further, we discuss the role of subjective experiences in fear, coding of fear memory as part of autobiographical memory and autobiographical memories in fear-related disorders. Finally, the development of linguistic tools for assessments and treatment of fear learning and memory disorders and how they might be valuable for basic and translational purposes in the area of fear learning and memory is discussed.

1.1. Definition of fear

Fear is defined as "a: an unpleasant often strong emotion caused by anticipation or awareness of danger; b (1): an instance of this emotion; (2): a state marked by this emotion" (Merriam-Webster, 2017). In line with recent arguments by LeDoux and Hofmann (2018), here we restrict the use of the term 'emotion' to subjective experiences. In their recent review, LeDoux and Hofmann refer to this view of fear as a subjective emotional experience as the *neuro-cognitive approach*, in which subjective fear emerges from higher-order processing. This view in turn is based on arguments that emotional experiences are "cognitive constructions based on conceptualizations of situations (Barrett, 2006, 2017; Barrett and Russell, 2015) or higher-order states that emerge as a result of the cognitive integration in working memory of diverse sources of information from within the brain and body (LeDoux, 1996, 2002; LeDoux, 2015a; LeDoux and Brown, 2017). LeDoux and Hofmann further argue that verbal self-report of fear is the gold standard in assessing conscious subjective emotional experiences including fear. As such, since verbal self-report is not an option for non-human organisms, determining whether non-human organisms have subjective experience of fear is difficult (LeDoux and Hofmann, 2018). However, non-human organisms do experience fear-related physiologic and behavioral states. It is in this context that our understanding of the biological processes involved has progressed most significantly over the last several decades.

1.2. The human emotion of fear

An organism's detection of potential threat involves innate biological processes that exist across the phylogenetic evolutionary spectrum (LeDoux, 2014). Much of what we have learned about how the human brain processes threat has been learned from animal models in which similar mechanisms operate (LeDoux, 1996). There are, however, important distinctions between the environmental detection of threat and the conscious experience of human fear. Simply put, threat detection is only one process within the complex emotional experience of fear, worry, and anxiety that comprise human states of being (LeDoux, 2014). The human brain, with its developed higher cortical regions, allows for the activation of threat detection systems and ultimately fear and anxiety through both external and internal cues. External cues are elements in the environment that can pose a threat to the health, integrity, and existence of an individual person (*e.g.*, venomous insects and animals, heights, or a social aggressor). Internal cues include bodily states (*e.g.*, arousal) in addition to the thoughts that are produced through our cognitive abilities. In other words, as humans, our threat detection systems and subsequent feelings extend beyond "is that dangerous" into numerous "what if" scenarios that include potential sources of harm (*e.g.*, illness, bodily injury).

Threat detection and defensive response behaviors are typically based on situation-specific factors such as the proximity, intensity,

immediacy, and probability of an aversive outcome (Blanchard et al., 1998; Diamond et al., 1999). For example, a rodent will freeze in its cage when presented with a sound or light that has been previously paired with an electric shock in the same cage (Davis, 1992). In this experimental example, the proximity, intensity, immediacy, and probability of an ensuing shock and its associated pain are well controlled and the behavior of the rodent is highly predictable (it will freeze in defense or flee depending on the options made available). In other words, the rodent will act in a manner consistent with what it has previously learned. As humans, our perception of these four factors is more complex and can be manipulated by internal and external cues as previously described.

As defined by LeDoux, fear can be defined as a state that occurs "when the sentient brain is aware that its personal well-being (physical, mental, social, cultural, existential) is challenged or may be at some point" (LeDoux, 2014, p. 2876). Human fear includes awareness that danger is near or possible, and in many types of human fear this can activate the basic threat detection systems (phobia, panic, heights). The mammalian response to threat involves the recruitment of the autonomic nervous system to alter physiological activity (*e.g.*, breathing, heart rate, blood pressure (Kapp et al., 1979; Schneiderman et al., 1974)) and endocrine systems to activate hormone release (*e.g.*, cortisol, epinephrine (Yehuda and McEwen, 2004)). A common thread between lower mammals and humans in this regard is that these systems are activated in order to increase the odds that the organism will survive a threatening cue or situation (Fanselow and Lester, 1988; LeDoux, 2012). One of the key discriminating factors between lower mammals and humans is the activation of non-conscious threat detection systems and the very human conscious feelings of fear, anxiety, and worry (for in-depth discussion see recent work by LeDoux (LeDoux, 2012, 2014). The experience of human fear as an emotion (as well as the etiology and treatment of fear-based disorders) occurs as a result of the complex interaction between the activation of basic threat detection systems, memory storage and retrieval, and our own conscious awareness. A primary clinical presentation of the factors described in the preceding section occurs in the aftermath of an experienced traumatic event and the associated long-term psychobiological consequences.

2. Human studies of fear learning and memory

2.1. Prefrontal cortical involvement in fear memory

Human neuroimaging studies represent a significant amount of research conducted on fear learning and memory (for reviews see Fullana et al., 2016; Gilmartin et al., 2014; LaBar and Cabeza, 2006). While at times this research can offer disparate views of conceptualized "emotion" and "cognitive" neural mechanisms, more recently, distributed processing perspectives suggest that these concepts are not separable (Pessoa et al., 2002; Pourtois et al., 2013). Therefore, we present the brief and generalized view that fear memory is an interaction between neural regions considered to be traditionally more involved in cognition (*i.e.*, the dorsal and ventral lateral PFC; DLPFC, VLPFC, respectively), neural regions traditionally considered to be more involved in emotion (*i.e.*, the orbital frontal cortex and the ventral medial PFC; OFC, VMPFC, respectively), as well as neural regions that span both concepts (anterior cingulate cortex; ACC) (Fig. 1). It is implausible that any of these regions act in isolation, but rather in concert to provide rich contextual ensembles of fear memory. Because this brief overview concerns PFC mechanisms of fear memory, the amygdala and hippocampus fall outside the scope of this section. However, the understanding and association of PFC regions involved in fear memory can be better viewed from the standpoint of functional and anatomical connectivity with the amygdalar/hippocampal complex. Specifically, much of PFC integration with fear memory relies on consensus that the proximal instantiation of fear memory occurs by interaction between the amygdala and hippocampus, beginning by the signaling of stimuli that are associated with, or predictive of, fear, which induces long-term potentiation (LTP) of amygdala–hippocampal circuits to upregulate encoding processes (LeDoux, 2003; McGaugh, 2004; Rogan et al., 1997). Therefore, to illustrate the PFC's involvement with fear memory, we provide a brief framework that outlines lateral PFC regions traditionally examined in the cognitive domain and medial PFC regions, traditionally examined either in the emotion domain or spanning both domains. Lastly, we incorporate these domains to understand the integration across the PFC during the acquisition of fear.

To begin, we first summarize research that outlines brain regions that traditionally have been investigated using cognitive tasks or are theoretically motivated by understanding cognitive processes, namely

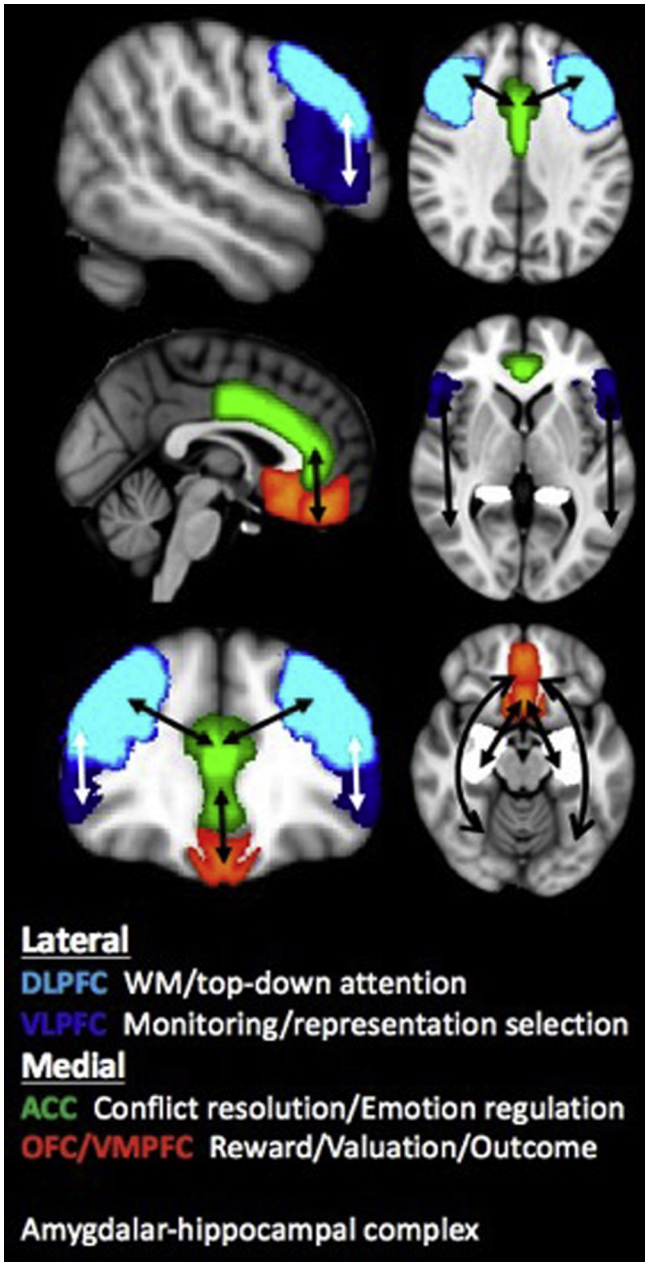

Fig. 1. Lateral and medial reresentation of PFC regions involved in the integration of fear memory. DLPFC, dorsolateral prefrontal cortex (light blue); VLPFC, ventrolateral prefrontal cortex (dark blue); ACC, anterior cingulate cortex (green); OFC, orbitofrontal cortex (orange); VMPFC, ventromedial prefrontal cortex (orange); amygdalar–hippocampal complex (white). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

memory and attention. Neuroimaging research indicates that lateral PFC (LPFC) regions become more active and are predictive of remembering, and thus indicative of encoding, during episodic and semantic memory operations (Buckner and Koutstaal, 1998; Gabrieli et al., 1996; Reisberg and Heuer, 2004). Additionally, research indicates that the DLPFC is likely engaged in maintaining working memory representations used to guide goal driven behavior in a top-down manner (Cohen et al., 1997; D'Esposito, 2001). Conversely, the VLPFC may be more involved in communication between posterior cortex for access to, and resolve interference between, competing semantic representations (Buckner et al., 1995). Moreover, neuroimaging work indicates that the LPFC is involved with the general allocation of attention, including a dorsal attentional system (DLPFC and superior parietal) that maintains goal representations of "what" and "where" to attend, and a ventral system (VLPFC and inferior parietal) that detects or monitors sensory representations consistent with goals to induce further processing (Corbetta et al., 2008; Corbetta and Schulman, 2002). Lastly, success at either attention or memory tasks appears to involve coordination between the more anterior regions of DLPFC and VLPFC, suggestive of communication between the two systems to accomplish task related goals (Shulman et al., 2009). Taken together, regardless of whether the processes under investigation are labeled "memory" or "attention", it is sufficient to say that both must interact or are largely inseparable when considering subsequent acquisition of information, hence memory relies on attention. Furthermore, within the LPFC, there appears to be a segregation of processes between higher-order goal representation regions (working memory maintenance, general attention) of the DLPFC and lower-order access to sensory or semantic representations (monitoring, selection) held in posterior cortex consistent with the VLPFC.

Turning to neuroimaging research conducted on learning and memory during emotion processing indicates canonical memory/attention LPFC neural mechanisms discussed above, as well as distinct medial brain regions, most prominently the OFC and VMPFC. Inconsistency surrounds the exact anatomical demarcation between the OFC and VMPFC in neuroimaging literature and lies outside the scope of this section. Therefore, we will generally refer to the orbital frontal and ventral medial regions as OFC/VMPFC. Neuroimaging research indicates that the OFC/VMPFC is consistently activated when affective stimuli are presented during tasks that involve attention or memory (Armony and Dolan, 2002; Perlstein et al., 2002; Pessoa, 2008). Specifically, a compendium of research indicates that the OFC/VMPFC is sensitive to reward-prediction and the expectancy of appetitive and aversive properties of stimuli (Hikosaka and Watanabe, 2000; Pessoa, 2008; Schneider and Brueckner, 2000). Facilitated by dense anatomical connections with the nucleus accumbens/ventral striatum and the amygdala, representing the mesolimbic dopamine pathway, the OFC/VMPFC lies in a position to represent the reward and thus, affective value of stimuli (Goldman-Rakic and Selemon, 1986). The OFC/VMPFC has also been shown to connect to inferior regions of temporal cortex to access semantic and sensory representations and maintains expectation of reward (Summerfield and Egner, 2009). Moreover, due to its position as the most anterior region in reward processing pathways, research indicates that the OFC/VMPFC is activated to maintain the outcome of reward and value prediction (Knutson and Cooper, 2005). Therefore, it is likely that when a stimulus is evaluated for its reward or affective value, the OFC/VMPFC receives and maintains information about the prediction and its outcome, putatively for higher-order brain regions to access and incorporate with current task/goal demands, and subsequently make adjustments (Pessoa, 2008; Ridderinkhof et al., 2004).

Spanning both cognitive and emotion domains, the ACC was first associated with cognitive processes during the bourgeoning of neuroimaging (Botvinick et al., 1999; Kerns et al., 2004). However, through extensive research it has been incorporated into models of emotion and motivation for at least the last decade (Ochsner and Gross, 2005; Rushworth et al., 2004; Vogt, 2005). General consensus suggests that roughly dividing (anatomically and functionally) the ACC into rostral and caudal regions, reflects its involvement in cognitive-emotion processes, respectively (Bush et al., 2000). In general, the rostral ACC has been linked to cognitive interference (*i.e.*, conflict monitoring and response conflict), which when high, is thought to signal the need for increased cognitive control (Botvinick et al., 1999; Kerns et al., 2004). The caudal ACC has been related to emotion related processes, such as detecting emotional stimuli (Vuilleumier et al., 2001), and most prominently in the control or down-regulation of emotion through its subgenual connections with the amygdala (Drevets, 2001). Therefore, it is likely that the more rostral regions of the ACC are involved in detecting and resolving conflict of on-going goal related activity *via* anatomical connections to the DLPFC, while caudal regions may be sensitive to conflict arising from emotion or affective value of stimuli in the environment, perhaps by modulation of affective circuits (*e.g.*, amygdala).

Taken together, a general framework for fear memory, then incorporates the previously mentioned neural mechanisms to indicate the interaction between cognition and emotion, as a seamless function. Importantly, none of the brain regions are isolated to "emotion" or "cognition" processes; rather, they exist on a continuum of integration depending on their anatomical and functional connectivity. Putatively, higher-order execution and allocation of top-down attention consistent with goal representation is maintained by the DLPFC. Because of its anterior-dorsal position, the DLPFC contains little anatomical connection with primary sensory processing regions (Mesulam, 1998). Mesulam (1998), while the VLPFC, *via* anatomical connection with posterior sensory cortex, is in position to monitor information in memory or the environment through lower-order bottom-up processing of such representations consistent with goal attainment (Pandya and Yeterian, 1985; Simons and Spiers, 2003). Through anterior VLPFC-DLPFC anatomical connections monitoring and alerting of sensory information is updated to select, attend and maintain relevant representations. Similarly, because the DLPFC contains little anatomical connection with the amygdala (Phelps, 2006), reward/affective value is integrated through more ventral pathways to the OFC/VMPFC through its connection with the mesolimbic dopaminergic pathway (*i.e.*, ventral striatum, nucleus accumbens; Goldman-Rakic and Selemon, 1986). This evaluative information can be thus maintained and transmitted through anatomical connection to the ACC to signal saliency (Haber et al., 2006), which subsequently can signal phasic shifts to up- or down-regulate attention and goal maintenance *via* connections with the DLPFC. Therefore, while the DLPFC may represent the most abstract, higher-order goal representation, due to its lack of direct connectivity with sensory cortex and regions that represent reward or affective value, this information is integrated and conveyed *via* OFC/VMPFC and the ACC, respectively. The convergence of these processes signals, "what" and "where", fear is represented in the environment, which induces continued or up-regulated processing *via* connections with the amygdalar-hippocampal complex for encoding.

Finally, all regions/circuits/pathways are integral to the ultimate learning and memory of a fear stimulus or context. Top-down goal representation (*e.g.*, be careful when moving in the dark) is held at the highest level by the DLPFC, which increases general attention allocation to environmental contexts. The VLPFC thus monitors sensory representations for selection of attention and continued processing (*e.g.*, is that a predator's shape?). While simultaneous reward or affective valuation from the OFC/VMPFC (*e.g.*, predatory shape is of high reward) can be maintained and transmitted *via* the ACC (*e.g.*, possible threat in the environment) to increase top-down control or alter goal representation (*e.g.*, be careful, or run away). The consequence of this cascade is that stimuli and contextual elements within the environment will be more greatly attended to and encoded for future reliance.

2.2. Human syndromes of impaired fear learning and memory

There are several human syndromes of impaired fear learning and memory that are known for some time. One is the relative rare Kluver-Bucy syndrome involving injury to both anterior temporal lobes (Lanska, 2018). Among a lot of other symptoms, patients lack emotions of fear. Patients with amygdala damage have impairments to recognize and express emotions, including impairments to remember an emotional event (Chau and Galvez, 2012). In nonhuman primates, amygdala lesions were shown to alter the social hierarchy (Rosvold et al., 1954). Los of dominance was also seen in violent prison inmates in Japan following surgical removal of their amygdalae (Narabayashi, 1972).

Some concepts about fear learning and memory have also been around for some time. About fifty years ago, the division of the amygdala in a dorsomedial division involved in defensive mechanisms following stimulation with the basolateral division playing an inhibitory role was already described (Fonberg, 1968). In addition, over forty years ago, it was described that predation affects sleep patterns, including sleep duration (Allison and Cicchetti, 1976).

2.3. Memory for positive and negative events

Over the past decades, there has been increased interest in understanding how individuals remember events that evoke affective reactions, with many theories proposed to explain the often-complex effects of emotion on memory. The vast majority of these theories have focused on effects of the *arousal* elicited by the event—the psychophysiological responses and subjective feeling of excitement or agitation—and have emphasized the processes that unfold as the event is initially processed and consolidated. These theories have led to many important insights as to the effects of emotion on memory, including the often-focal effects of arousal on memory, enhancing some aspects of memory while having no benefit on others (see Table 1).

There is a smaller, yet consistent, literature that has revealed differences in the ways that positive and negative events are remembered, even when these events are associated with similar levels of arousal. Behaviorally, negative events are often remembered more vividly (*e.g.*, Dewhurst and Parry, 2000; Ochsner, 2000) and with more specific detail (*e.g.*, Holland and Kensinger, 2012; Kensinger and Schachter, 2008) than are positive events.

Most research examining the basis for these valence differences has focused on encoding processes, revealing that sensory processing is disproportionately enhanced during the encoding of negative information whereas conceptual processing is disproportionately engaged during the encoding of positive information (*e.g.*, Mickley Steinmetz and Kensinger, 2009). More generally, negative affect is thought to encourage an analytic focus on event-specific details (Storbeck and Clore, 2005, 2011), perhaps enabling the individual to hone in on what has gone wrong or on where a threat lies (Levine and Bluck, 2004). By contrast, pleasure seems to encourage a broadening of attention (Fredrickson, 2001) and a heuristic or conceptual mode of processing (Clore et al., 2001; Levine and Edelstein, 2009), perhaps because with no problem to be solved, creative processing can be prioritized (Bless et al., 1996). Interestingly, despite age-related changes in memory for positive relative to negative events (Mather, 2012), the increased sensory specificity of negative relative to positive memories may remain present across the adult lifespan (*e.g.*, Holland and Kensinger, 2012; Kensinger and Schachter, 2008; Kensinger et al., 2007).

Recent research has suggested that this sensory specificity of negative memories can be linked to the way that sensory processes are brought on-line again at the moment of retrieval. Multiple studies have shown greater activation in ventral visual processing streams during the retrieval of negative as compared to positive memories (*e.g.*, Markowitsch et al., 2003; Piefke et al., 2003). Importantly, these differences can exist even if those events are cued by neutral content (Bowen and Kensinger, 2016; Kark and Kensinger, 2015). In Kark and Kensinger (2015), participants viewed negative, positive, and neutral images from the International Affective Picture System (Lang et al., 2008). Later, at retrieval, their memories for those images was cued with relatively neutral black-and-white line-drawing outlines of those images. Memory for negative stimuli was associated with greater reactivation of the visual regions recruited during encoding than was memory for positive or neutral stimuli, and this overlap was additionally linked to memory confidence. Bowen and Kensinger (2016) replicated these findings: participants studied neutral words in the context of negative, positive, or neutral faces or scenes and their memories were later cued with those neutral words. There was greater reactivation within the ventral visual processing stream during the successful retrieval of neutral words that had previously been studied in negative contexts compared to positive or neutral contexts. Importantly, there was no emotion present in the retrieval cues (all were neutral words), and thus these valence differences in recapitulation must have been related to differences in the brain states triggered by

Table 1
Prominent theories of emotional memory that focus on importance of arousal.

	Theory	Brief summary of theory
Encoding	Automatic or rapid processing (Ohman, 1979; Pourtois et al., 2013)	Arousing information is oriented toward automatically and benefits from rapid processing.
	Prioritization of processing (Pessoa, 2005)	Arousing information is more likely to be prioritized for processing than neutral information.
	Cue-Utilization Hypothesis (Easterbrook, 1959)	As emotional arousal increases, there is a restriction in the range of cues that are used or attended.
Encoding and post-encoding	Post-Stimulus Elaboration (Christianson, 1992)	Arousing information is elaborated and rehearsed.
	Memory Trade-Offs; Weapon-Focus Effect (Barrett, 2006; Loftus et al., 1987)	Some aspects of an arousing event are remembered well, at the expense of other aspects.
	Arousal Biased Competition (Mather and Sutherland, 2011)	Arousal creates a "winner-take-more" state, biasing processing toward the information that gains high priority *via* bottom-up or top-down influences.
	Mediation Theory of Emotional Memory Enhancement (Talmi, 2013)	Arousal re-allocates attentional and organizational resources.
	Emotional Binding (Yonelinas and Ritchey, 2015)	Item-emotion binding by amygdala leads to slower forgetting than item-context binding by hippocampus.
Storage	Memory Modulation (McGaugh, 2000)	Arousal activates the amygdala and engages adrenergic and cortisol systems to promote memory storage.
Retrieval	Response Bias (Dougal and Rotello, 2007)	Arousal causes individuals to be more liberal in endorsing a memory.
	Subjective Sense of Recollection (Phelps and Sharot, 2008)	Amygdala engagement during retrieval biases individuals to experience a sense of recollection.

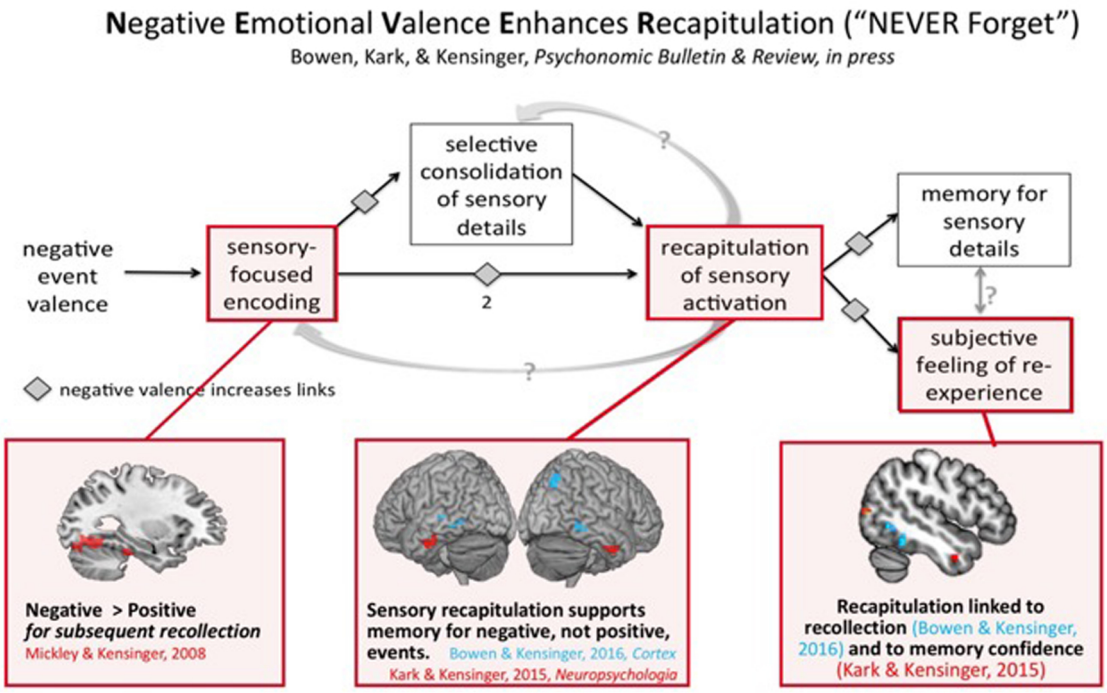

Fig. 2. A novel model to represent the encoding and retrieval of positive and negative memories. This model highlights the importance of considering negative valence during all stages of memory, and how negative emotions at any point may affect the memory's strength.

the emotion during encoding. Using a partial least squares analysis of that dataset, it was additionally revealed that there was a valence effect at retrieval, which was one of the dominant patterns in the data (Bowen and Kensinger, 2017), despite the fact that there was no emotion inherent in the retrieval cues.

These results place new emphasis on differences in the ways that positive and negative events are retrieved. While there is no doubt that emotion affects the way that events are experienced, encoded, and initially consolidated (McGaugh, 2000; Murty et al., 2011), these results demonstrate the importance of considering longer time-courses for the effects of emotion on memory. Based on these results, a new model was developed, Negative Emotional Valence Enhances Recapitulation, with the mnemonic "NEVER Forget." This model builds off of the evidence that negative valence has effects on encoding, storage, and retrieval (see Fig. 2) and emphasizes the importance of considering effects of emotional valence that extend past the initial encoding episode to influence how sensory processes are integrated into emotional memory networks.

3. Translational studies of fear learning and memory in humans and animal models

3.1. Neurocircuitry involved in extinction of fear memory in rodents; translational studies in humans

An inability to suppress inappropriate fear responses is the hallmark of fear-based disorders, such as PTSD (Rauch et al., 2006; Rosen and Schulkin, 1998). A common, empirically-validated approach to treat PTSD is Prolonged Exposure Therapy (PE) (Foa, 2011), one component of which involves repeated exposure to fear-linked cues to produce "extinction" of fear (clinically referred to as exposure leading to desensitization) and to prevent avoidance responses to these cues (Hofmann, 2008). This exposure-based learning can be modeled in the laboratory, in both animals and humans, using Pavlovian fear conditioning models in which fear is first linked to a previously innocuous cue (conditioned stimulus; CS) and then decreased by presenting the CS alone (producing extinction). Unfortunately, one major limitation of extinction is that it is a temporary phenomenon and extinguished fear can re-emerge with the passage of time (spontaneous recovery), as a result of a change in experimental context (renewal shift), or by exposing subjects to an aversive unconditioned stimulus (US) after extinction (reinstatement effect) (Bouton, 2004; Bouton et al., 2006; Hermans et al., 2006; LaBar and Phelps, 2005; Meyers and Davis, 2007; Milad et al., 2005; Robbins, 1990; Vansteenwegen et al., 2005). Together, these findings suggest that extinction is a new learning process, and fear reduction results from an inhibition rather than an erasure of the original fear memory (Bouton, 2002). Fear extinction and its recall have become the prime translational neuroscience target for the treatment of PTSD and other anxiety disorders (Graham and Milad, 2011; Jovanovic and Ressler, 2010; Milad and Quirk, 2012).

Convergent evidence from rat and human work has elucidated that discrete, yet anatomically and functionally interconnected, brain structures are critical for extinction learning and the retention of extinction memory (Fig. 3). Critical brain regions include the amygdala, ventromedial prefrontal cortex (VMPFC), and hippocampus (Amano et al., 2010; Bouton et al., 2006; Corcoran et al., 2005; Davis and Whalen, 2001; Kalisch et al., 2006; LeDoux, 2000; Meyers and Davis, 2007; Milad and Quirk, 2002; Milad et al., 2006b, 2007; Ochsner and Gross, 2005; Pape and Pare, 2010; Pare et al., 2004; Phelps, 2004; Quirk and Beer, 2006; Quirk et al., 2006, 2003; Quirk and Mueller, 2008). During fear acquisition, sensory information about the CS and the aversive US converge at the amygdala and become associated, yielding the fear memory. This memory is subsequently translated into conditioned responses of fear (CRs) (Davis and Whalen, 2001; LeDoux, 2000). Of note, the amygdala may also be involved in extinction learning (Amano et al., 2000; Pape and Pare, 2010). Indeed, functional magnetic resonance imaging (fMRI) studies in humans have correlated amygdala activation with fear CRs during conditioning (LaBar and Phelps, 2005; Phelps, 2004; Phelps et al., 2001). Prefrontal brain regions that interconnect with the amygdala, particularly the infralimbic cortex in rats and the VMPFC, a homologous structure in humans, are important for the retention and retrieval of extinction memories and consequent attenuation of fear CRs perhaps *via* inhibition of amygdala output neurons (Milad and Quirk, 2002; Ochsner and Gross, 2005;

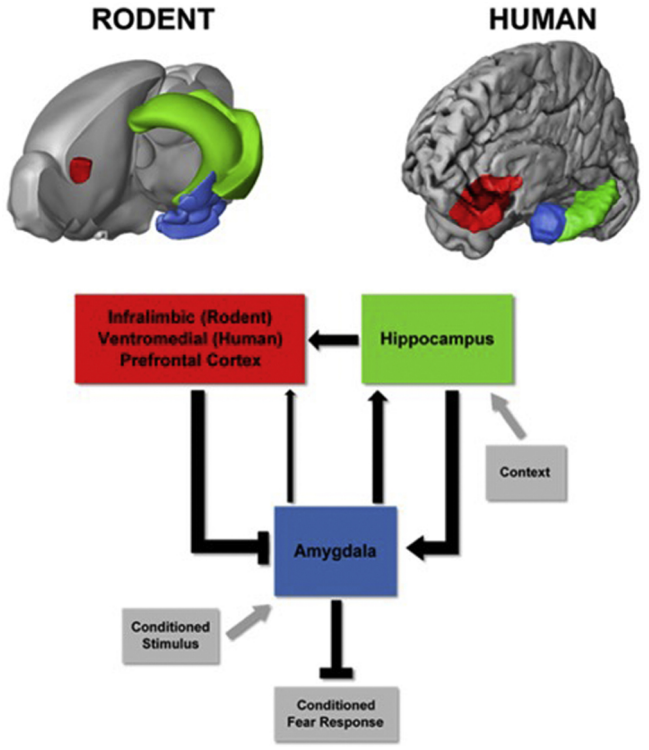

Fig. 3. Fear extinction neural circuitry and functional brain model during recall of extinction learning. *Top*. Brain regions involved in fear extinction include the infralimbic cortex [rodents]/ventromedial prefrontal cortex [humans] (red), hippocampus (green), and the amygdala (blue). Rodent and human anatomical models were created using the Allen Mouse Brain Atlas (Lein et al., 2007) and the Allen Human Brain Atlas (Hawrylycz et al., 2012), respectively. *Bottom*. During fear acquisition, sensory information about the conditioned stimulus (CS) and the aversive unconditioned stimulus (US) converge at the amygdala and become associated, yielding the fear memory. The fear memory is then subsequently translated into conditioned fear responses. Prefrontal brain regions that interconnect with the amygdala, particularly the infralimbic cortex in rats and the ventromedial prefrontal cortex, a homologous structure in humans, are important for the retention and retrieval of extinction memories and consequent attenuation of conditioned fear responses perhaps *via* inhibition of amygdala output neurons. It has been hypothesized that the hippocampus controls the context-dependent renewal of conditioned fear responses by regulating activity within the amygdala either indirectly *via* projections to the infralimbic cortex/ventromedial prefrontal cortex and/or through direct projections to the amygdala. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Phelps, 2004; Quirk and Beer, 2006; Quirk et al., 2003; Quirk and Mueller, 2008) (Fig. 3). In rats, infralimbic cells display robust CS-elicited activity during extinction recall, which is inversely correlated with spontaneous recovery of fear CRs (Milad and Quirk, 2002). Indeed, artificial stimulation of infralimbic cells in rats during extinction learning strengthens extinction memory and attenuates spontaneous recovery of extinguished fear during subsequent tests of extinction recall (Milad and Quirk, 2002). In humans, VMPFC activation during extinction recall and VMPFC thickness are both positively correlated with the magnitude of extinction retention (Hartley et al., 2011; Milad et al., 2005, 2007; Phelps et al., 2004). In addition, the magnitude of task-dependent functional coupling between the amygdala and VMPFC has been shown to be negatively correlated with intensity of subjective reports of negative affect (Banks et al., 2007).

Activation of the hippocampus is also involved in recall of extinction learning and the hippocampus mediates the context-dependent renewal of extinguished fear (Kalisch et al., 2006; Milad et al., 2007) (Fig. 3). In rodents, temporary inactivation of the hippocampus prior to extinction learning prevents the expression of fear extinction when tested in either the extinction context or in a different context (Corcoran et al., 2005). It has been hypothesized that the hippocampus controls the context-dependent renewal of fear CRs by regulating activity within the amygdala, either indirectly *via* projections to the VMPFC (Hoover and Vertes, 2007) and/or through direct projections to the amygdala (Henry et al., 2008). In humans, hippocampal activation is associated with successful retrieval of extinction memory and is positively correlated with VMPFC activation during extinction recall in humans (Kalisch et al., 2006; Milad et al., 2007). Interestingly, increased functional connectivity between the amygdala and the hippocampus has been attributed to the persistence of memories for emotionally arousing events in humans (Hamann et al., 1999; Kilpatrick and Cahill, 2003a, 2003b; Murty et al., 2011; Phelps et al., 2004; Ritchey et al., 2008).

More recently, the default mode network (DMN), an intrinsic connectivity network anchored in the VMPFC and precuneus/posterior cingulate cortex, has been implicated in fear extinction. One recent fMRI study suggests that that the DMN, and particularly the VMPFC, is activated by cues signaling safety, but not those signaling danger (Marstaller et al., 2017). Further, in that study, activity in the DMN was inversely correlated with activity in brain regions associated with the expression of fear CRs (*i.e.*, dorsal anterior cingulate cortex, insula), and was positively correlated with self-rated positive affect evoked by cues that signal safety. These findings have led to the hypothesis that the DMN, and the VMPFC in particular, is involved in the contextualization of safety memories and in determining the most adaptive response to the present situation (*e.g.*, fight or flight). Taken together, these separate lines of convergent evidence suggest that how these regions interact with one another may mediate the control, or lack thereof, of fear CRs in humans.

Dysfunction in fear circuitry has been a consistent finding in PTSD neuroimaging studies, and is thought to play a role in the maintenance of trauma memories. In particular, many studies have shown amygdala hyperactivity in PTSD in response to both trauma-related and unrelated negative stimuli (Bryant et al., 2008; Driessen et al., 2004; Hendler et al., 2003; Liberzon et al., 1999; Morey et al., 2009; Pissiota et al., 2002; Protopopescu et al., 2005; Rauch et al., 2000; Shin et al., 1997, 2004a, 2005; Vermetten et al., 2007; Williams et al., 2006). Exaggerated amygdala reactivity in patients with PTSD may be due, in part, to insufficient top-down regulation from the VMPFC. Insufficient VMPFC may, in turn, lead to hyperarousal and deficits in extinction retention, as well as an impaired ability to suppress attention and responses to trauma-related stimuli (Liberzon and Phan, 2003; Pitman et al., 2001; Rauch and Shin, 1997; Rauch et al., 1998). Consistent with this notion, studies have shown that exaggerated amygdala reactivity is associated with lower responses in the VMPFC across individuals with PTSD (Shin et al., 2004a, 2005). Although less commonly implicated, abnormal hippocampal function and diminished hippocampal volumes in PTSD patients have been associated with deficits in contextual processing, as well as memory impairments and neuroendocrine dysregulation (Bonne et al., 2001; Bremner, 1999; Bremner et al., 2003; Shin et al., 2004a, 2006, 2004b; Werner et al., 2009). Poor extinction recall and VMPFC-hippocampal dysfunction displayed by patients with PTSD could undermine the efficacy of the therapeutic effects of exposure (Charney and Deutch, 1996; Foa, 2000; Milad et al., 2008, 2009; Orr et al., 2000; Pitman et al., 2001; Rougemont-Bucking et al., 2011; van Minnen and Hagenaars, 2002); evidence of aberrant activation in fear circuitry in humans with PTSD indicates a mechanism that directly impacts PE success, since treatment relies on activation of fears (Pitman et al., 2001; Rougemont-Bucking et al., 2011; Milad et al., 2008).

Although PE is an effective first-line treatment for PTSD, approximately 20–30% of patients who have completed treatment continue to have a PTSD diagnosis, and a slightly higher percentage (30–40%) fail to achieve a stringent criterion for good end-state functioning (Foa et al., 1999; Rothbaum et al., 2005). In addition, a significant subset of patients fail to complete treatment (20.5%) (Hembree et al., 2003). An

even smaller number of patients respond to first-line pharmacological treatments, such as selective serotonin reuptake inhibitors (SSRIs) (Stein et al., 2009, 2006). In 2007, the Institute of Medicine concluded that little empirical evidence exists to support current pharmacological treatment for PTSD; therefore, new treatments are desperately needed (IOM, 2007). Enhancing the neural and neurochemical substrates of inhibitory fear learning could solve this challenge and improve PTSD treatment outcomes (Graham and Milad, 2011; Jovanovic and Ressler, 2010; Milad and Quirk, 2012).

Various adjuncts have proven their potential as "cognitive enhancer" *via* an enhancement of extinction learning and its consolidation (for a review, see Kaplan and Moore, 2011). One of the first compounds assessed for this role was D-cycloserine (DCS), which increases glutamate function in the brain. Animal studies have demonstrated that administration of DCS before or after extinction learning results in better extinction memory recall when tested 24 h later (Richardson et al., 2004; Walker et al., 2002). While initial clinical studies of DCS reported some promise when coupled with exposure therapy sessions (Hofmann et al., 2006; Ressler et al., 2004), some more recent findings suggest that DCS may be ineffective or even more harmful by enhancing reconsolidation of the fear memory rather than the extinction memory (Bolkan and Lattal, 2014; Lee et al., 2006; Rothbaum et al., 2014). Nonetheless, research on DCS has paved the way for examining other neurobiological targets that may be more effective for augmenting the learning that occurs during exposure-based therapies. One such promising system is the cannabinoid system. Animal studies have shown that pharmacological inactivation of type 1 cannabinoid receptors (CB1) blocks the consolidation of fear extinction, suggesting that CB1 receptor activation is critical for extinction learning and/or its later recall (Reich et al., 2008). Pharmacological enhancement of cannabinoid signaling has shown promise in human studies as well (Das et al., 2013; Rabinak et al., 2014, 2013). For example, a randomized double-blind placebo-controlled, between-subjects design in healthy adults, Rabinak and colleagues demonstrated than an acute dose of Δ9-tetrahydrocannibinol (THC), a CB1 receptor agonist, administered prior to extinction learning increased neural activation of the hippocampus and VMPFC during extinction recall, tested 24 h after extinction learning (Rabinak et al., 2014). Another promising system is the estrogen system. Studies in rodents show that increasing estrogen levels during or immediately following extinction learning increases c-fos activity in the infralimbic cortex, and decreases c-fos activity in the amygdala. In line with these results, elevated endogenous or exogenous levels of estrogen in women is associated with better extinction memory recall (Zeidan et al., 2011; Graham and Milad, 2013).

3.2. Neural mechanisms involved in fear learning and memory; focus on the role of serotonin in animal models and humans

In this section, we consider the role of important neuromodulators of fear-related physiologic and behavioral states, with a focus on serotonergic systems.

3.2.1. Serotonergic systems and neuromodulation of fear-related physiologic and behavioral states

Serotonergic systems modulate a number of fear-related physiologic and behavioral responses and states. In some cases, the role of serotonergic systems on different fear-related behavioral responses is unequivocally opposite. For example, serotonergic systems are thought to facilitate anxiety-like and fear-related behavioral responses, but, in contrast, to inhibit escape or panic-like behavioral responses (Abrams et al., 2004; Hale et al., 2012; Hale and Lowry, 2011; Hassell et al., 2017; Lowry et al., 2008; Lowry and Hale, 2010; Zangrossi and Graeff, 2014). On the surface, opposing effects of serotonergic systems on different fear-related behaviors should not be surprising as some fear-related behaviors are mutually exclusive. For example, freezing behavior, which is commonly observed during innate fear-related responses to predators or other imminent threats, and which is commonly observed in cue- or context-dependent models of Pavlovian fear conditioning, is incompatible with panic- or escape-like behavioral responses. What is shared among all of the fear-related behavioral responses and behavioral states is that they are considered defensive behavioral responses (*e.g.*, freezing, hiding, risk assessment, flight, and defensive threat/attack), which are those behavioral responses observed in the presence of a real or perceived threat (Blanchard and Blanchard, 2008).

3.2.2. Serotonergic systems and innate fear-related responses

Rodents respond to the presence of a perceived threat, *e.g.*, shock or predator odor, with innate avoidance and freezing behavior (Silva et al., 2016; Takahashi et al., 2005), or startle responses (Brocke et al., 2006). Evidence suggests that these innate fear-related behavioral responses are modulated by serotonergic systems. Serotonergic neurotransmission is regulated by the sodium-dependent, high affinity, low capacity, presynaptic serotonin transporter, encoded by the *SLC6A4* gene. The serotonin transporter clears serotonin from the synapse, consequently determining the duration and extent of serotonergic synaptic neurotransmission (Blakely et al., 1994; Torres et al., 2003). In humans, allelic variation in a 44-base pair insertion/deletion polymorphism in the serotonin transporter gene promoter region (5-HTT gene-linked polymorphic region or 5-HTTLPR) results in long (l) and short (s) variants. The s allele is associated with reduced transcriptional efficacy, and, consequently, lower serotonin transporter expression, leading to reductions in serotonin re-uptake and increased extracellular serotonin concentrations (Greenberg et al., 1999). Studies of eye blink startle responses revealed that carriers of the s allele responded with greater startle responses relative to l/l homozygotes (Brocke et al., 2006). These data suggest that serotonin may enhance innate fear-related startle responses. Consistent with these findings, the 5-HT receptor agonist meta-chlorophenylpiperazine (mCPP) dose dependently increases acoustic startle responses in rats (Fox et al., 2008). Although exposure to predator odor has been associated with increased serotonin metabolism in the central nucleus of the amygdala, an important mediator of fear-related behavioral responses (Hayley et al., 2001), little is known about the functional role of serotonergic signaling in control of innate freezing responses to predator odor or other threats. Determining the role of serotonergic systems in innate fear responses such as freezing behavior remains an important objective for future studies.

3.2.3. Serotonergic systems and conditioned fear-related responses

There is a general consensus that the amygdala plays an important role in the acquisition, storage, and expression of cued fear-related behavioral responses, while the hippocampus plays an important role in encoding the contextual environment and the prefrontal cortex plays an important role in modulating the expression of fear-related behavioral responses (for review, see Davis and Whalen, 2001; LeDoux, 2000). The role of serotonergic signaling in the amygdala, with a focus on the basolateral amygdala, on fear acquisition and fear expression in Pavlovian fear conditioning models has recently been reviewed (Bocchio et al., 2016). Briefly, there is some evidence that serotonergic neurons modulate basolateral amygdala circuits during fear conditioning, but there is equivocal evidence for phasic, time-locked, activation of serotonergic neurons by unconditioned and conditioned aversive cues (Bocchio et al., 2016). Given that serotonergic neurons have an anatomical and functional topographical organization (Imai et al., 1986), electrophysiological recordings of identified serotonergic neurons that project to the basolateral amygdala will be required to address this question. Nevertheless, similar to the effects of allelic variation in the 5-HTTLPR on innate fear responses, carriers of the s allele show enhanced fear-potentiated startle, relative to l/l homozygotes (Klumpers et al., 2012), suggesting that serotonin may enhance fear-potentiated startle responses. Overall, the weight of the evidence from both human and

non-human animal studies supports the hypothesis that serotonin acts within the basolateral amygdala to enhance fear acquisition, and, possibly, fear expression (Bocchio et al., 2016). Studies also support a role for serotonergic signaling in control of fear extinction (Narayanan et al., 2011). Future studies are required to fully elucidate the role of serotonergic signaling in the basolateral amygdala and the extended fear circuitry in fear acquisition, fear memory consolidation, fear expression, fear extinction, spontaneous recovery of fear, and reinstatement of fear.

3.2.4. Serotonergic systems and risk-assessment or conflict anxiety-related responses

Risk assessment or conflict anxiety-like behavior is a fear-related, defensive behavior that involves a high level of uncertainty in relation to aversive outcomes (Blanchard and Blanchard, 2008). In many cases, anxiety-related behavioral responses are associated with conditions that involve a conflict between approach and avoidance, in situations that involve both potential rewarding outcomes and potential aversive outcomes (Lowry and Hale, 2010; Gray, 1982). An example in humans might be a high school junior asking a high school senior out on a date to Prom. In such situations, there is clear potential for either a rewarding or aversive outcome, creating a conflict and apprehension or anticipatory anxiety that may lead to avoidance.

Studies in rodents have demonstrated that anxiogenic drugs, anxiety-related neuropeptides, and other anxiogenic stimuli increase expression of c-Fos, encoded by the immediate-early gene, *FOS*, within serotonergic neurons located in the dorsomedial part of the dorsal raphe nucleus, a region with dense projections to the basolateral amygdala and anxiety- and fear-related circuitry (Abrams et al., 2004; Hale et al., 2012; Hale and Lowry, 2011; Hassell et al., 2017; Lowry et al., 2008, 2005; Lowry and Hale, 2010; Zangrossi and Graeff, 2014). Pharmacologic, lesion, and other approaches are consistent with a role for serotonin, acting *via* 5-HT_{2C} receptors within the basolateral amygdala, in facilitation of anxiety-related behavioral responses and anxiety states (Lowry et al., 2005).

On the other hand, evidence suggests that serotonergic neurons in the median raphe nucleus play a role in the resolution of anxiety- or fear-related behavioral responses (Forster et al., 2006, 2008). Recognizing this topographical specificity of anxiogenic stimuli on serotonergic systems is important, as it suggests that understanding the role of serotonergic systems in control of anxiety- and fear-related behavioral responses will require approaches that take into account this high level of specificity (*e.g.*, recordings from anatomically or functionally identified subsets of serotonergic neurons).

3.2.5. Serotonergic systems and panic-related or escape responses

In stark contrast to the evidence that posits that serotonin projections originating from the dorsal raphe nucleus and projecting to the basolateral amygdala enhance anxiety-like behavioral responses, there is overwhelming evidence suggesting that serotonin projections originating from the dorsal raphe nucleus and projecting to the dorsal periaqueductal gray inhibit escape or panic-like behavioral responses *via* actions at 5-HT_{1A} and 5-HT_{2A} receptors (Hassell et al., 2017; Spiacci et al., 2016; Zangrossi and Graeff, 2014). Consistent with these findings, Tph2 mutant mice ($Tph2^{-/-}$) respond with increased escape-like behaviors to associative footshock (Waider et al., 2017). Recent studies have demonstrated that escape responses in the presence of a looming threat are under control of a retinoraphe projection originating from a subset of retinal ganglion cells (RGCs). In this model, looming signals transmitted by RGCs projecting to the dorsal raphe nucleus activate local GABAergic neurons that in turn inhibit serotonergic neurons (Huang et al., 2017). Inhibition of serotonergic neurons that tonically inhibit escape behaviors would be expected to disinhibit escape behaviors and enable successful escape from threat. These findings highlight the importance of understanding the complexity of serotonergic effects on fear-related physiologic and behavioral responses when envisioning novel therapeutic strategies for treatment of stress-, anxiety-, and trauma-related disorders.

3.2.6. Serotonergic systems and defensive threat/attack responses

Very little is known about the effects of serotonergic signaling on defensive threat/attack responses in the presence of a perceived threat. However, this promises to be a fruitful area for future research as blockade of 5-HT_{2C} receptors within the medial hypothalamus or dorsal periaqueductal gray, critical structures involved in defensive threat behaviors (Keay and Bandler, 2010), prevents stimulated defensive threat responses (Bhatt et al., 2008; Hassanain et al., 2003a, 2003b).

3.2.7. Serotonergic systems and stress-induced enhancement of fear-related responses

In addition to the role of serotonergic signaling in modulation of fear-related physiologic and behavioral responses described above, serotonin is also critical in stress-induced enhancement of fear-related physiologic and behavioral responses, for example in a model of learned helplessness (Maier and Watkins, 2005). This effect is thought to be dependent on desensitization of inhibitory 5-HT_{1A} autoreceptors that normally inhibit serotonergic neuronal firing within the anxiety- and fear-related dorsomedial part of the dorsal raphe nucleus (Maier and Watkins, 2005; Rozeske et al., 2011). Thus, serotonergic systems may play a role in normal, adaptive fear-related physiologic and behavioral responses, and also stress-induced exaggeration of these responses.

3.2.8. Serotonergic systems and stress-, anxiety-, and trauma-related disorders

With a life-time prevalence of up to 20% of the population, stress-, anxiety-, and trauma-related disorders, including PTSD, are common and represent a significant social and economic burden (Kessler et al., 1995, 2005a; Wittchen et al., 2011). A major risk factor for the development of trauma-related and anxiety disorders is exposure to stressful life events (Pemberton and Fuller Tyszkiewicz, 2016; Zavos et al., 2012). One mechanism through which adverse events may affect risk for stress-related psychiatric disorders is through effects on brainstem serotonergic systems (Valentino and Commons, 2005). These effects might involve the role of serotonin in sleep, including serotonin release during slow-wave sleep (Lapierre et al., 2013), and the circadian rhythms of sleep-wake cycles (Makamaru-Osigo, 2012). Further characterization of the role of serotonergic systems in control of fear-related physiologic and behavioral responses, and stress-induced exaggeration of these responses, should enable development of novel therapeutic strategies for the prevention and treatment of stress-, anxiety-, and trauma-related disorders that involve dysregulation of fear.

3.3. Neural mechanisms involved in fear conditioning and extinction; focus on the role of norepinephrine in animal models and humans

The locus coeruleus (LC) is a is a bilateral brainstem nucleus that is the main source of norepinephrine (NE) projections within the central nervous system (Aston-Jones and Waterhouse, 2016). It is also the primary source of cortical NE (Giustino and Maren, 2018) and highly relevant for fear and learning because of the many LC projections (Schwarz and Luo, 2015; Schwarz et al., 2015) that extend to the medial prefrontal cortex, the basolateral amygdala (all nuclei), the central amygdala and the hippocampus (Foote et al., 1983). Locus coeruleus norepinephrine (LC-NE) plays an important role in the formation and retrieval of emotional memories (Raio and Phelps, 2015; Rodrigues et al., 2009), a topic that we discuss below.

3.3.1. Noradrenergic systems and neuromodulation of fear-conditioning

The LC is active in response to both appetitive and aversive stimuli (Foote et al., 1983; Zhang et al., 2014a). Several studies show that LC-NE is important for cued fear conditioning (*c.f.*, Uematsu et al., 2017).

Decreasing NE with clonidine results in dose-dependent reductions in fear expression while increases in NE (with piperoxane or yohimbine) increase fear expression (Davis et al., 1979; Schulz et al., 2002). Under high levels of stress, increased LC-NE produces corresponding increases in amygdalar NE which promotes cued fear learning by enhancing amygdala function and blunting prefrontal function, but under low levels of arousal, the LC-NE promotes PFC function while inhibiting the amygdala and promoting the extinction of cued fear (Arnsten, 2015; Giustino and Maren, 2018).

Notably, the central amygdala is reciprocally connected to the LC (Van Bockstaele et al., 1998) and it activates the LC *via* corticotropin-releasing hormone under stress (Prouty et al., 2017). Since the central amygdala is important for fear expression and involved in freezing behaviors (*via* the periaqueductal gray) (Fadok et al., 2017; Haubensak et al., 2010), this feedback loop appears to be a way to generate sustained fear responses, especially after fear conditioning (Giustino and Maren, 2018).

There is also some evidence to suggest that LC-NE may be important for contextual fear learning as well. For example, the depletion of NE results in impaired contextual fear (Hott et al., 2012; Murchison et al., 2011; Onaka et al., 1996) while increased levels of NE promote contextual fear learning (Hu et al., 2007; Kim et al., 1997). But a recent study has shown that reduced NE in the central amygdala reduces the acquisition of context fear (Holmes et al., 2017) so the precise role of NE in contextual fear learning is still not fully understood.

The hippocampus integrates spatial information which is also important in context fear conditioning (Maren et al., 2013). The hippocampus is also densely populated with β-adrenoceptors which regulate long-term potentiation when activated by NE. In general terms, lower levels of NE appear to facilitate memory retrieval while higher levels promote long-term episodic memory (Harley, 2007). It is therefore believed that long term potentiation in the hippocampus is modulated by variations in NE (Lim et al., 2017) and that it is important for contextual fear acquisition.

3.3.2. Noradrenergic systems and fear expression

NE is also involved in the modulation of fear expression as well. Early studies with rodents revealed that experimentally decreasing NE could produce dose-dependent reductions in fear expression whereas increases in NE could produce corresponding increases in fear expression (Davis et al., 1979; Schulz et al., 2002). Some studies using single shock conditioning have not produced consistent results (*i.e.*, reduced NE has had no effect), but it was recently discovered blocking NE transmission disrupts multi-trial, but does not disrupt single-shock, conditioning (Diaz-Mataix et al., 2017). Similarly, NE levels impact contextual fear expression as well. Reducing NE produces deficits in context fear retrieval (Murchison et al., 2011, 2004) whereas increases in NE enhance context fear expression (Inoue et al., 2006).

3.3.3. Noradrenergic systems and memory

While NE is involved in the formation of cued fear memories (Uematsu et al., 2017) it may not be critical for consolidation of such memories. Research has shown that mice lacking NE do not have deficits in cued fear memory consolidation (Murchison et al., 2004; Ouyang and Thomas, 2005) and manipulations (reductions) of NE in the medial prefrontal cortex (Fitzgerald et al., 2015) and basolateral amygdala (Bush et al., 2010) also have no apparent impact on fear memory consolidation (Giustino et al., 2017). On the other hand, NE appears to be centrally involved in contextual fear memory consolidation. Increased NE enhances contextual fear memory consolidation, an effect that can be reversed by blocking NE with propranolol (Gazarini et al., 2013, 2014).

Reactivated memory has been shown to be a flexible state (Nader et al., 2000), and within this process, NE also has a role to play in memory reconsolidation (for both cued and contextual fear memories). For example, reduced NE has been shown to disrupt memory reconsolidation of both cued and contextual fear memories in rodents (Debiec and LeDoux, 2004; Gamache et al., 2012; Przybyslawski et al., 1999).

3.3.4. Noradrenergic systems and fear extinction

The hippocampus, basolateral amygdala and ventromedial prefrontal cortex all participate in the extinction of inhibitory avoidance and contextual fear conditioning (Fiorenza et al., 2012). It is also generally believed that stress-related increases in NE impair cued fear extinction (Debiec et al., 2011; Giustino et al., 2016; Rosa et al., 2014). For example, studies have shown that reduced NE impairs delayed fear extinction (Fitzgerald et al., 2015; Mueller et al., 2008) and increased NE enables delayed fear extinction (Debiec et al., 2011; Mueller et al., 2009).

NE also has an important role in contextual fear extinction as well, an action that appears to be reliant upon hippocampal function. Blocking norepinephrine transporter enhances the extinction of contextual fear in a dose-dependent manner (Abraham et al., 2012) whereas reduced NE has been shown to impair the extinction of contextual conditioned fear responses (Bernardi and Lattal, 2010; Do-Monte et al., 2010).

3.3.5. Noradrenergic systems and stress-, anxiety-, and trauma-related disorders

Increases in NE and corticotropin-releasing hormone (CRH) are a well-established aspect of the stress response. CRH projections from the central amygdala promote LC-NE activity during stress, which in turn evokes acute anxiety responses as well as place aversion (Sun et al., 2015). This, combined with the fact that many LC projections (Schwarz and Luo, 2015; Schwarz et al., 2015) extend to the medial prefrontal cortex, the basolateral amygdala, the central amygdala and the hippocampus (Foote et al., 1983), and the fact that locus coeruleus norepinephrine (LC-NE) plays an important role in the formation and retrieval of emotional memories (Raio and Phelps, 2015; Rodrigues et al., 2009) make it highly relevant for PTSD. Increases in the noradrenergic signaling have been implicated in PTSD (Hendrickson et al., 2018; Naegeli et al., 2018) and persistent changes in LC function have been observed following stress/trauma (Blanchard et al., 2012; George et al., 2013). These increases in NE are believed to support a “hyperconditioning” response to fearful stimuli while also supporting a general impairment in fear extinction (Norrholm et al., 2015; VanElzakker et al., 2014).

3.4. Emotional olfactory fear memory during development and adulthood; animal models

3.4.1. Olfaction: particularities and advantages for studying memory and emotions

Olfactory stimuli are of prime importance throughout the life of both human and non-human mammals. They regulate ethologically vital behaviors such as feeding (reviewed in Palouzier-Paulignan et al., 2012), orientation of the infant toward its caregiver (Al Ain et al., 2014; Coureaud et al., 2010; Varendi and Porter, 2001), maternal behavior (Corona and Levy, 2015; Lundstrom et al., 2013; Schaal et al., 1995), or choice of a mating partner (Brennan et al., 1990; Edwards et al., 1990). Supporting this pivotal role from very early infancy to adulthood, the olfactory sensory system becomes functional *in utero*, thus ensuring the transition between prenatal and postnatal environments (Mennella et al., 2001; Pedersen and Blass, 1982; Schaal et al., 1998). This is particularly important for rodent pups that are born blind, deaf and hairless, and are critically dependent on odor cues to approach their mother and attach to her nipples to get food and warmth.

The olfactory sensory pathways present a unique organization among the sensory systems. Indeed, the olfactory bulb, first relay of olfactory information, sends direct projections to the olfactory cortex, without a thalamic relay (Haberly and Price, 1977). In parallel, the

olfactory bulb sends dense projections to the cortical amygdala nuclei, which project to the deeper basolateral nucleus (McDonald, 1998; Savander et al., 1996). In addition, the olfactory bulb also makes monosynaptic contacts with the lateral entorhinal cortex, which projects to the hippocampus (Witter and Amaral, 1991). This anatomical organization illustrates that olfactory information has a unique rapid access to two structures critically involved in emotion and memory, *i.e.* the amygdala and hippocampus.

The vast majority of studies devoted to investigate the neural circuits of emotional memory in animals have used cued fear conditioning that involves pairing an initially neutral tone with a mild footshock. After a few such pairings, the animal develops a conditioned fear response to the tone itself. Fear conditioning has been abundantly used in adult rodents to investigate the neurobiology of learning and memory and there is a broad consensus in this literature that the amygdala plays a crucial role in the acquisition, storage and expression of cued fear memories, while the hippocampus is involved in encoding the contextual environment, and the prefrontal cortex in modulating the expression of fear responses (for reviews see: Davis, 1992; LeDoux, 2000; Maren, 2001). A main advantage of cued fear conditioning paradigm is that it can also be applied to infants because it makes very little demand on the animal's motoric capabilities. Since newborn rodents are blind and deaf but perform very well with odors, odor fear conditioning provides a unique opportunity to highlight differences in the formation and expression of olfactory emotional memories through development.

3.4.2. Odor-shock conditioning from the early neonatal period to adulthood: from odor preference to odor fear

Although the olfactory system becomes functional during the latest stages of pregnancy, it continues to mature postnatally. For example, in rodents the olfactory bulb's volume increases 7 times during the first 30 days, as it acquires the majority of its inhibitory interneurons (Rosselli-Austin and Altman, 1979). Similarly, in the first days of life, the amygdala is quite immature and different studies have shown profound morphological and physiological changes during the first postnatal month (Berdel et al., 1997; Chareyron et al., 2012; Ehrlich et al., 2012; Ryan et al., 2016) followed by dendritic remodeling at adolescence (Koss et al., 2014). The hippocampus and prefrontal cortex also exhibit delayed morphological (Crain et al., 1973; Verwer et al., 1996) and physiological (Bekenstein and Lothman, 1991; Nair et al., 2001; Nurse and Lacaille, 1999; Swann et al., 1990) developmental profiles and their maturation continues through adolescence (Dumas, 2005; Tarazi and Baldessarini, 2000; van Eden et al., 1990).

This protracted development of the brain suggests the rodent neonate has a unique circuitry for odor processing and learning that is relevant to the continuously changing ecological context throughout development. During their first two weeks of life, rodent pups are mostly confined to the nest and strongly depend on their functional olfaction to get access to milk, warmth and maternal care. Consequently, at this developmental age, infant rodents exhibit strong odor preference learning abilities presumably allowing them to attach to their caregiver for survival (Cheslock et al., 2000; Sullivan et al., 1989). Interestingly, in rat pups under 10 days of age, learned preference is also observed even when the odor is paired with a painful stimulus such as tail pinch or mild electric footshocks (Camp and Rudy, 1988; Sullivan et al., 2000a). Thus, the same procedure that induces learned odor fear in adult rats (*i.e.*, odor-shock pairing) produces odor preference in infant rats. This seemingly paradoxical pain-associated preference is supported by neurobiological mechanisms that ultimately promote preference regardless of the quality of parental care, thus ensuring attachment to the caregiver (Boulanger Bertolus et al., 2016; Perry et al., 2017; Raineki et al., 2010). Specifically, these mechanisms involve plastic changes in the olfactory bulb and anterior piriform cortex (Morrison et al., 2013; Roth and Sullivan, 2005; Sullivan and Leon, 1986; Wilson et al., 1987; Yuan et al., 2002). In the olfactory bulb, these changes are allowed by unique characteristics of infants' locus coeruleus functioning, resulting in the release of high amounts of norepinephrine (Nakamura et al., 1987) that are both necessary and sufficient to produce learned odor preference (Sullivan et al., 2000b, 1992; Yuan et al., 2002). In rat pups under 10 days of age, the amygdala

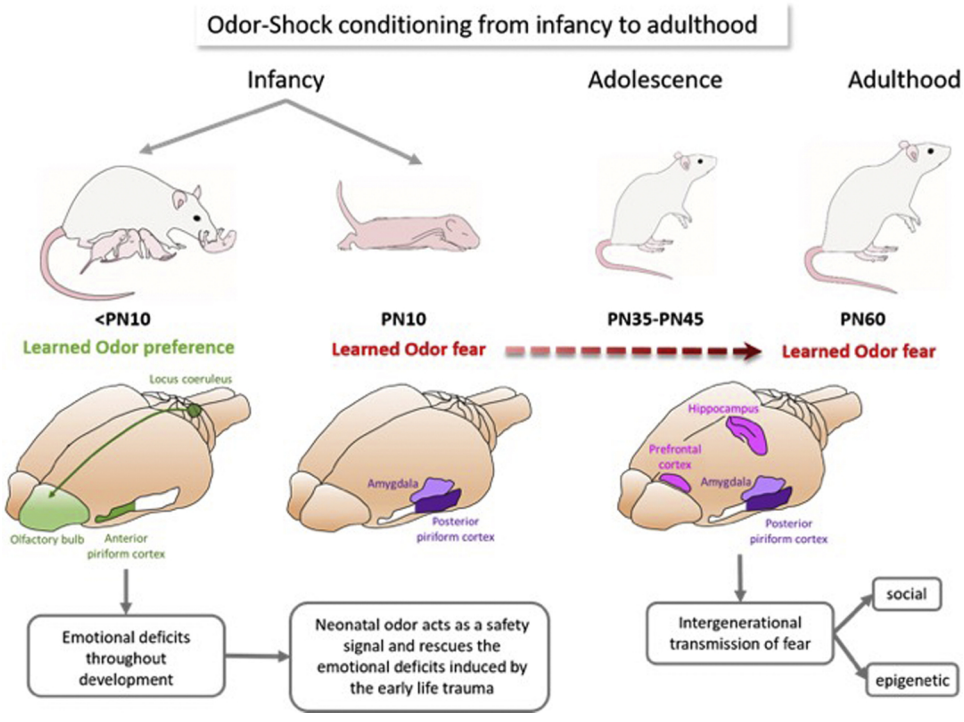

Fig. 4. Main behavioral and neurobiological characteristics of odor fear conditioning through development. *Left panel.* In infant rat pups under the age of postnatal (PN) day 10, odor-shock training induces a learned odor preference and involves a neural circuit including the olfactory bulb and the anterior piriform cortex with a unique functioning of the locus coeruleus resulting in the release of high amounts of norepinephrine (involved brain regions and unique input of locus coeruleus on the olfactory bulb indicated in green). *Middle panel.* From the age of PN10, odor-shock training induces adult-like learned odor fear that is sustained by a circuit involving the amygdala and the posterior piriform cortex (involved brain regions indicated in purple). *Right panel.* As the pup grows older and reaches adolescence and adulthood, other structures mature and can modulate the learning such as the prefrontal cortex and the hippocampus progressively mature and are able to modulate the learning (involved brain areas indicated in pink). Besides resulting in odor preference, early life odor-shock stressful experience also induces emotional deficits throughout development that can be rescued by the odor learned during the neonatal period (for details, see main text). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

is not recruited by the odor-shock association learning. This period of life is characterized by reduced corticosterone and ACTH release in response to mild stress and is referred to as the stress hyporesponsive period (SHRP) (Levine, 2001). Importantly, intra-amygdala corticosterone infusion before training enables precocious odor-aversion learning and increases amygdala neural activity similar to that seen in older pups (Moriceau et al., 2006).

As the pup grows older, its locomotion develops and its ecological niche extends beyond the nest with potential exposure to danger, such as encounters with predators. Concomitantly, the behavioral response to odor-shock conditioning shifts from approach/preference to avoidance/fear of the learned odor (Camp and Rudy, 1988; Sullivan et al., 2000a). This shift coincides with the end of SHRP, with increasing levels of corticosterone in response to stress. *Via* its action within the amygdala, corticosterone plays a decisive role in the emergence of learned odor fear. Indeed, decreasing corticosterone levels in the amygdala at this age turns the behavior back to preference learning (Moriceau et al., 2006). Therefore, from postnatal day 10, the amygdala gets involved in the learning, as well as the posterior piriform cortex while the anterior piriform cortex is no longer recruited (Moriceau and Sullivan, 2004; Moriceau et al., 2006; Raineki et al., 2009). This transition toward a more adult-like behavioral response and underlying network continues with the pup maturation (Fig. 4).

In adult animals, the role of the amygdala in odor fear learning has been confirmed in several studies for the different phases of memory formation: acquisition, consolidation and recall (Cousens and Otto, 1998; Hegoburu et al., 2014, 2009; Kilpatrick and Cahill, 2003b; Rosenkranz and Grace, 2002; Sevelinges et al., 2004, 2007, 2008). Besides the central role of the amygdala, many other structures participate in the network underlying odor fear learning, going from peripheral sites to highly integrative areas as summarized in Table 2.

Among these different areas, the olfactory piriform cortex plays a privileged role at different steps of the learning. For instance, it is involved during the very first trials of the acquisition session through increases in glutamate release (Hegoburu et al., 2014), as well as during memory consolidation as replay of activity patterns imposed in the olfactory cortex during post-training slow wave sleep were shown to enhance the subsequent strength of memory (Barnes and Wilson, 2014) In addition, Sacco and Sacchetti (2010) reported that excitotoxic lesions of olfactory secondary sensory cortex impaired remote, but not recent, odor fear memories in rats. This result has been confirmed using transient blockade of NMDA receptors in the piriform cortex prior to the training session (Hegoburu et al., 2014). Together these data suggest that the piriform cortex is an ideal locus to combine the sensory characteristics of the stimulus with its affective learned value transmitted by projections from the amygdala, and initiate the long-term storage of the various attributes of the learned odor. Thus, due to its distinctive anatomy, the olfactory system constitutes a particularly relevant model for studying the relative contribution of sensory cortices and amygdalar nuclei to memory processes.

3.4.3. Long-lasting effects of odor-fear conditioning

3.4.3.1. Effects of neonatal experience on adult emotional and cognitive abilities. It is well known in the literature of development that early life maltreatment has deleterious effects on later life cognitive and emotional processing. Therefore, although the pairing of an odor with a shock before the age of 10 days induces a learned odor preference in rat pups, this adverse treatment also has long-lasting adverse consequences for the individual. Repeated odor-shock pairings have been shown to model maternal maltreatment (Raineki et al., 2010) and to induce social behavior deficits in juvenile rats, both toward the mother (Rincon-Cortes et al., 2015) and toward peers (Raineki et al., 2012). These deficits persist at adolescence, at which age they are associated with depressive-like behaviors that are maintained until adulthood (Raineki et al., 2012; Rincon-Cortes et al., 2015; Sevelinges et al., 2011). These alterations seem to be mediated in part by a dysregulation of the amygdala (Raineki et al., 2012; Rincon-Cortes et al., 2015; Sevelinges et al., 2011, 2007, 2008). Importantly, the learned attraction displayed by pups toward the odor associated with shock persists into adulthood, which confers to this odor the ability to rescue the trauma-induced depression-like behaviors observed in adolescent and adult rats (Raineki et al., 2012; Rincon-Cortes et al., 2015; Sevelinges et al., 2011). In addition, it reduces fear-associated neural activity (Sevelinges et al., 2007), suggesting that it has endorsed the properties of a safety signal (Pollak et al., 2008).

3.4.3.2. Effects of parental experience on subsequent generations. Odor-fear conditioning in adulthood leads to the learning of the odor as a threat signal. This learned fear is long lasting and recent data have shown that it can be transmitted across generations. Indeed, exposing a mother to a learned fearful odor in presence of her pups is sufficient to induce a learned fear to that odor in pups, even before they develop the ability to learn fear through odor-shock pairing (Debiec and Sullivan, 2014). This learning is maintained at least into adolescence, suggesting that maternal fear conditioning can have long-term consequences on the offspring. The highly specific experience of fear conditioning can also be transmitted to the offspring through non-social mechanisms, *via* epigenetic inheritance. Indeed, the offspring of both first and second generations of male mice conditioned to fear a specific odor shows increased sensitivity to that odor (Dias and Ressler, 2014). This suggests that odor fear conditioning in parents can be transmitted to the first generation through social fear learning but also to the next generations that have never been exposed to the odor, *via* epigenetic changes. Intergenerational transmission of fear is also observed in humans where it can play an important role in the transmission of maladaptive fears and anxiety (Bowers and Yehuda, 2016). This passage of fear from one generation to the next has been observed in offspring of Holocaust and 9/11 survivors, with progeny showing higher risk to develop PTSD and generally express higher anxiety and lower self-esteem (Bowers and Yehuda, 2016; Gangi et al., 2009).

Table 2
Structures involved in odor fear conditioning in rodents.

Structure	References
Olfactory sensory neurons	Dias and Ressler (2014); Kass et al. (2013)
Olfactory bulb	Dias and Ressler (2014); Fletcher (2012); Kass and McGann (2017)
Olfactory cortex	Hegoburu et al. (2009, 2014); Sacco and Sacchetti (2010); Sevelinges et al. (2004, 2008, 2011)
Amygdala	Cousens and Otto (1998); Hegoburu et al. (2009, 2014); Kilpatrick and Cahill (2003b); Sevelinges et al. (2004, 2007, 2008)
Dorsomedial striatum	Boulanger Bertolus et al. (2014)
Perirhinal cortex, hippocampus	Herzog and Otto (1997); Otto and Poon (2006)
Prefrontal cortex	Laviolette et al. (2005); Awad et al. (2015)

3.4.4. Possible avenues for translational studies

Several studies have investigated the networks involved in fear conditioning in human using functional brain imaging. Most of these studies show that the amygdala is part of the circuit, thus corroborating the data from the animal literature (for a review see Phelps and LeDoux, 2005). Only a few studies have used odor fear conditioning in the literature. Among them, Li et al. (2008) reported that aversive olfactory learning enhances perceptual acuity of the sensory signal. Indeed, initially indistinguishable odor enantiomers become discriminable after aversive conditioning. In parallel, functional brain imaging revealed that the amygdala response to the conditioned odor increases sharply in early trials. Interestingly, the authors also measured changes in activity in the piriform cortex. They reported that spatial patterns of activity in posterior piriform cortex were highly correlated between the two enantiomers before conditioning, but became distinct after conditioning. Taken together these data indicate that aversive learning induces plasticity in posterior piriform cortex that correlates with increased odor enantiomer discrimination. The data obtained in human odor fear conditioning are strikingly similar to those described in rats and suggest that while the amygdala plays a crucial role, a broad network of structures is involved in the learning among which the piriform cortex seems to endorse a privileged status.

Although odors often trigger involuntary recall of pleasant autobiographic memories (Chu and Downes, 2002), they are also particularly powerful to be precipitants of anxiety and fear-related memories in patients with PTSD (Daniels and Vermetten, 2016). A better understanding of the formation and storage of odor fear memories throughout life might help developing new therapeutic tools to alleviate some of the symptoms of anxiety disorders such as PTSD. For instance, some odors are known to have calming and anxiolytic effects in both animals (de Sousa et al., 2015) and humans (Dong and Jacob, 2016). Additionally, delivery of odor contextual cues during sleep has been shown to modulate the strength of associative memories, *i.e.* enhance declarative memory and extinguish fear memory (Hauner et al., 2013; Oudiette and Paller, 2013; Shanahan and Gottfried, 2014). Exposure of PTSD patients to trauma-related odors during sleep might help reduce their level of anxiety and alleviate their daily life burden.

3.4.5. Conclusion on olfactory-related fear memory

The olfactory system is an evolutionarily old sensory system with a well-preserved neural circuitry, at least compared to other sensory systems, with direct access to brain structures involved in emotion and memory. Moreover, olfaction is functional at birth, thus suggesting that the sense of smell has a critical role in controlling behavior throughout life in mammals. The remarkable flexibility of the olfactory system to adapt to divergent learning demands as the animal grows and ventures outside the nest highlights the critical role of olfaction in the formation of emotional memories.

3.5. Role of genetic and environmental factors in fear memory in animal models; translational studies of genetic risk factors of PTSD severity in humans

Fear learning and memory in animal models is often studied using fear conditioning, passive or active avoidance, or fear-potentiated startle paradigms. In contextual and cued fear learning and memory, an environment (context) or cue (such as a tone) are combined with an aversive stimulus (such as a footshock) and fear learning, memory, and memory extinction can be assessed (Fanselow and Kim, 1994; Gerlai, 1998; Maren, 2001). Translational fear conditioning tests in humans are being used based on these animal tests (Milad et al., 2011). The passive avoidance test involves a two-compartment chamber with a connecting door; one chamber is lit, which is aversive to small animals, while the other remains dark (Beatty et al., 1973). The animal receives a slight footshock when it enters the preferred dark compartment and latency to re-enter in subsequent training or recall trials is assessed as a measure of fear memory. In fear potentiated startle, the animal's response to an acoustic stimulus is potentiated by including a footshock (Missig et al., 2010).

Importantly, the extinction of fear memory is often studied in the context of PTSD and forms the basis of exposure therapy. As noted, PTSD is one of the most common and debilitating anxiety disorders (Kessler et al., 1995, 2005b). The detrimental effects of PTSD are often magnified by accelerated development of stress-related medical conditions (Johnson et al., 2015). It is frequently comorbid with other mental disorders (Horesh et al., 2017), especially anxiety and depressive disorders and has been identified as a major unique identifier for suicidality (Krysinska and Lester, 2010). PTSD is characterized by the presence of four distinct symptom clusters: intrusion, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity (Pai et al., 2017). Following a traumatic event, many people experience traumatic stress symptoms, but rates appear to diminish quickly over the course of a few months. Thus, PTSD is a condition in which a positive course of recovery from trauma is impeded (Korol et al., 1999). It has been estimated that close to 90% of people are exposed to at least one traumatic event, such as rape, assault, disaster, rescue work, or combat, over the course of their lifetime, suggesting that there is something unique about those that continue on to develop PTSD.

As discussed previously fear conditioning is often used to study the inhibition or extinction of learned fear, a process believed to underlie the recurring and re-experiencing symptoms of PTSD (Kong et al., 2014). The phenomenon of recurring and persistent recall of traumatic memories in PTSD and related symptoms may be related to a failure of extinction learning (Charney et al., 1993; Charney and Nestler, 2005) or a failure to modify or acquire new associations to contextual stimuli (Lang et al., 2009). Based on these possibilities, conditioned fear has been widely used to study aspects of PTSD in humans and animal models (VanElzakker et al., 2014).

The prevalence of PTSD suggests the involvement of environmental risk factors, including socioeconomic status and education, and associations between intensity and number of traumatic events (Breslau et al., 1998, 1995; Kessler et al., 1995; Sledjeski et al., 2008; Xue et al., 2015). In animals, an example of an environmental risk factor is X-ray radiation: after mice were trained in a fear conditioning paradigm, they were exposed to X-rays and subsequently assessed for fear memory and extinction of fear memory. Post-training radiation exposure impaired extinction of both contextual and cued fear memory (Kugelman et al., 2016; Olsen et al., 2014).

In addition, there is support for a role for genetic risk factors of either developing PTSD or for severity of PTSD symptoms (Cornelis et al., 2010; Yehuda et al., 2011; Pitman et al., 2012). For example, twin studies have provided support for heritable and genetic risk factors increasing PTSD susceptibility (Kremen et al., 2012). Of the genes that have been linked to PTSD, the various isoforms of apolipoprotein E (apoE) are particularly intriguing (Kim et al., 2013; Freeman et al., 2005). ApoE is an essential component of lipoprotein particles in both the brain and periphery, and exists in three isoforms in the human population: apoE2 (E2), apoE3 (E3), and apoE4 (E4) (Mahley et al., 2000). ApoE plays numerous roles in behavioral and cognitive functions, including regulation of anxiety and cognitive performance during normal aging and in the context of neurodegenerative disease (Verghese et al., 2011; Raber et al., 2004; Raber, 2007). Several neurobiological functions associated with PTSD have been shown to be modulated by apoE isoform, including hippocampal volume (Hostage et al., 2013), cognitive impairment (Caselli et al., 2007), and neuroendocrine alterations related to the hypothalamic-pituitary-adrenal (HPA) axis (Gil-Bea et al., 2010; Peskind et al., 2001; Raber et al., 2000). Compared to E3, E4 has been associated with decreased brain metabolism (Reiman et al., 2004), deficient repair following injury (Laskowitz et al., 1998), and earlier onset and increased risk of Alzheimer's disease (AD); conversely, E2 is generally protective against

cognitive decline (Farrer et al., 1997; Olsen et al., 2012). However, E2 was associated with an increase in the risk and severity of PTSD (Kim et al., 2013; Freeman et al., 2005). In the first study, E2 was associated with an increased risk of PTSD and modulated the interaction between PTSD and alcohol use (Kim et al., 2013). In the second, E2 was associated with decreased memory function and more severe re-experiencing symptoms in chronic, combat-related PTSD subjects (Freeman et al., 2005).

Consistent with these two studies, it was recently demonstrated that homozygous mice expressing human E2 exhibit impaired extinction of contextual fear memory (Olsen et al., 2012). Several PTSD-like behavioral, cognitive and neuroendocrine alterations are more pronounced in mice expressing E2. These alterations include a resistance to exposure therapy (fear extinction), alterations in anxiety-like and home cage behavior, circadian disturbances, and hippocampus-dependent cognitive impairment following a stressful event. Importantly, data collected on the severity of PTSD symptoms in combat veterans were consistent with the mouse data. In a group of 92 veterans with combat-related PTSD, those with E2/E3 showed significantly higher Clinician Administered PTSD Scale (CAPS) and PTSD checklist (PCL) scores compared to E3/E3 and E3/E4 individuals. Alterations in salivary cortisol within this same group of E2/E3 veterans with PTSD were also identified. Together, these results support an important role for E2 in the pathogenesis of PTSD. While it is clear that genetic risks to develop PTSD exist, recent work demonstrates the importance of considering epigenetic mechanisms in susceptibility (Heinzelmann and Gill, 2013; Kwapis and Wood, 2014).

For a complete understanding of acquisition, formation, extinction of fear memory and individual risk to develop fear-related memory disorders, baseline genetic and epigenetic differences as well as gene-environment interactions need to be considered (Fig. 5). Personal writings prior to being exposed to a traumatic experience might help in identifying individuals at particular risk to develop a fear memory disorder. For example, astronauts write in personal journals during space missions. This important and rich information is being used to assess a wide range of emotional and psychological states and create a rank-ordering of behavioral observations (Stuster, 2016). Space missions, especially extended missions, provide a lot of insights into mental health and progression of mental health. Previous analysis of hand-written journals has successfully predicted future cognitive and

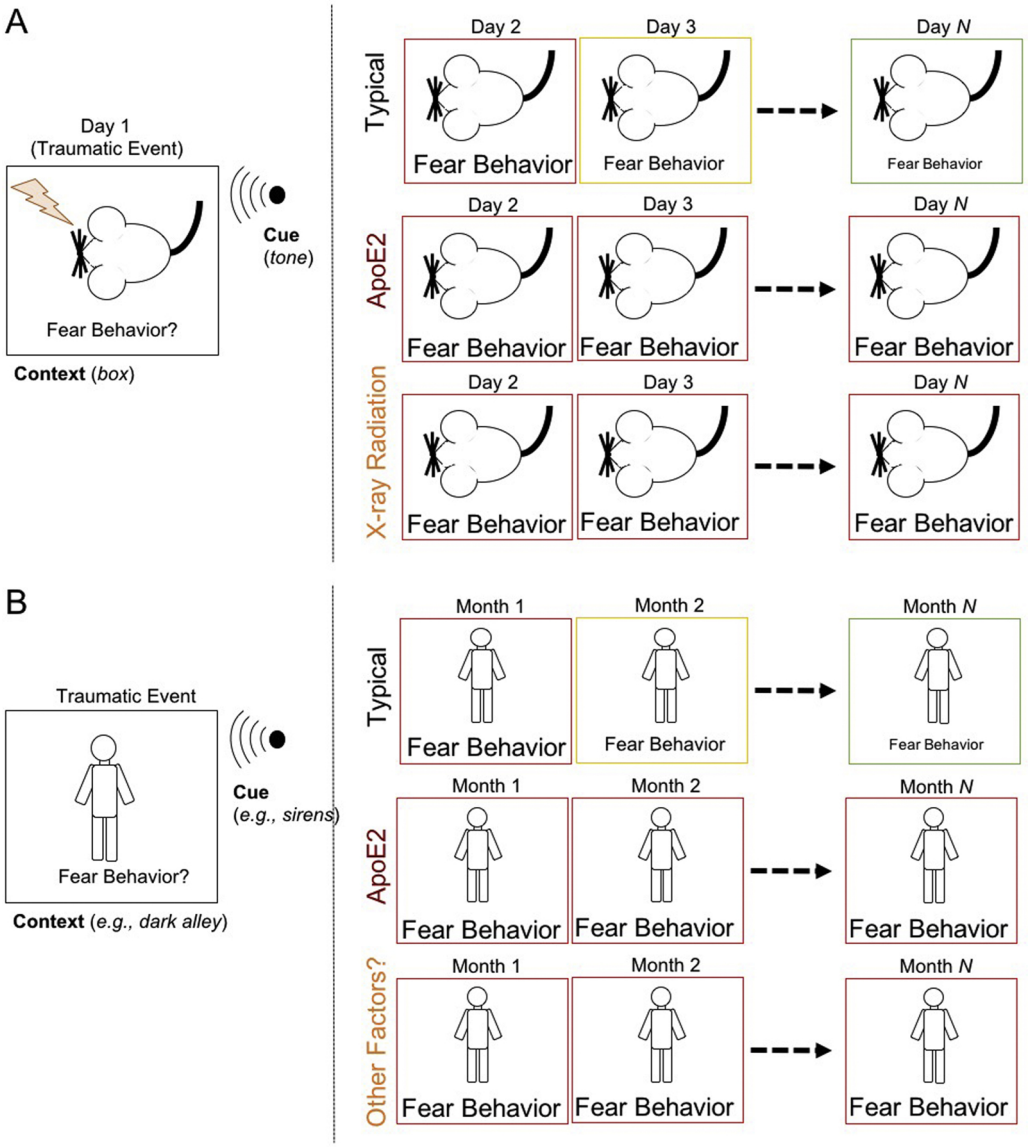

Fig. 5. Role of genetic and epigenetic factors as well as gene–environment interactions in acquisition, formation, and extinction of fear memory and individual risk to develop fear-related memory disorders in mice (A) and humans (B). The smaller font of fear behavior over time indicates extinction of the fear memory. The font of fear memory not changing indicates impaired extinction of fear memory.

emotional state. Handwriting complexity of nuns in their twenties was used to predict risk to develop dementia six decades later (Riley et al., 2005). More related to fear, handwritten autobiographies from nuns in their early twenties, were successfully analyzed for emotional content and related to survival during ages 75 to 95 (Danner et al., 2001). A strong inverse association was found between positive emotional content in the writings and risk of mortality in late life. Although important and very valuable, the journal entries and handwritings are subjective data. Therefore, it is important to combine these kinds of analyses with quantifiable objective outcome measures, as typically obtained in analysis of fear in humans and animal models. These subjective resources, in conjunction with objective measures, can be used in our multidisciplinary, collaborative effort in affective neuroscience to map the entire range of human feelings and emotions, allowing us to develop predictive analyses.

4. Development of treatments for fear learning and memory disorders

4.1. Fear learning paradigms and contributions to treatment of fear and anxiety disorders

4.1.1. Observing and quantifying human fear expression: common themes from "bench to bedside"

The development and symptomatology of stress-, trauma-, and anxiety-related disorders such as PTSD are frequently studied through the use of patient self-report measures. However, the reliability of these subjective indices can easily be compromised due to the high overlap between PTSD signs and symptoms and other mental disorders with which it may be co-morbid (*e.g.*, major depressive disorder, panic disorder, generalized anxiety disorder). This overlap makes it difficult for practitioners and clinical scientists to identify symptoms *specific* to the etiology and presentation of post-traumatic sequelae; relevant examples include shared symptoms of negative cognitions and mood that can complicate the assessment of PTSD, depression, and/or substance use and withdrawal (Brown, 1998). Fortunately, well-established, translational methodologies have emerged that allow clinical researchers to examine specific subclasses of symptoms in human fear and anxiety disorders. As discussed earlier, the most notable examples are fear learning paradigms that provide robust operationalization of the acquisition, extinction, and return of learned fears. Recent work employing fear learning paradigms has targeted the identification of trauma- and stressor-related deficits in fear learning as well as putative neurobiological risk factors for PTSD and related mental disorders (Briscione et al., 2014).

PTSD is a complex, heterogeneous disorder that spans several domains of a patient's daily experience including quality of life, emotional regulation, anger and irritability, and social functioning, however, central features of PTSD are mediated by impairments in learned fear metabolism (Norrholm and Jovanovic, 2010; Zuj et al., 2016). The experience of a traumatic event can be conceptualized as a brief, compressed, and durable form of fear acquisition, according to Pavlovian principles (Rothbaum and Davis, 2003). Exposure to a threat to one's integrity or survival (*e.g.*, combat trauma) serves as an unconditioned stimulus (US) that can evoke a psychobiological fear response in the absence of any previous learning. Environmental stimuli (*e.g.*, sights, sounds, smells of the Middle Eastern landscape for combat veterans and civilians) can acquire fear-eliciting properties based on their association with the unconditioned, unexpected, traumatic event. As a result, an individual who was present at the time of the pairing between the trauma and ambient surrounding stimuli may acquire a persistent fear to these cues (that can be termed conditioned stimuli (CS) experimentally or "triggers" clinically). Laboratory fear learning methods often include psychophysiological indices such as fear-potentiated startle, skin conductance, or heart rate variability, allowing investigators to observe and quantify this type of learning in traumatized human populations (Michopoulos et al., 2015).

In a typical translational fear conditioning paradigm, fear acquisition occurs when a previously neutral stimulus or CS, is repeatedly paired with an aversive outcome or US (*e.g.*, an aversive airblast to the larynx for humans (Norrholm et al., 2006) or cutaneous electric shock (Schiller et al., 2012). Similar to animal models, a widely used psychophysiological tool for studying human fear learning is fear-potentiated startle, in which the relative increase in the frequency or magnitude of the acoustic startle reflex is assessed before, during, and after an association is developed between a CS and US. This paradigm's clinical utility has substantiated from fear-potentiated startle methods that have been employed to characterize physiological responses accompanying exaggerated fear expression, contributing considerable data to clinical applications and treatment of PTSD and fear-related disorders (Norrholm et al., 2015).

Fear memories are not permanent and can be strengthened or weakened through laboratory and clinical methods that can alter the expression of conditioned fear (Myers and Davis, 2002). As expected, extinction learning is evident in fear-potentiated startle paradigms as a within- and between-session decrease in the intensity of the acoustic startle response during and following repeated, non-reinforced CS presentations (Norrholm et al., 2011a, 2006, 2008).

Fear extinction recruits a form of new learning in which an inhibitory memory trace associated with the previously reinforced CS competes with, but does not eliminate, the labile fear acquisition memory trace (Liberzon and Abelson, 2016; Myers and Davis, 2002). As described earlier, the original fear memory remains intact and is accessible through specific learning mechanisms identified as reinstatement (through unsignaled presentation of the previously used US; Bouton and Bolles, 1979; Rescorla and Heth, 1975), renewal (through a change in experimental context; Bouton, 1993), or through the passage of time (termed spontaneous recovery; Pavlov, 1927). Clinically speaking, the learning and memory principles of reinstatement, renewal, and spontaneous recovery are observed in symptom relapse following a change in environment (*e.g.*, from therapist's office to home), time elapsed since cessation of extinction-based treatment (*e.g.*, prolonged exposure therapy), or experiencing a stressful life event (*e.g.*, health crisis or subsequent trauma re-exposure), respectively (Briscione et al., 2014). It is important to note here that the return of an original fear memory following extinction learning can be readily observed in the laboratory (for examples see Norrholm et al., 2014, 2011b; Warren et al., 2014).

Fear extinction learning in humans represents a viable avenue for studying the acquisition, extinction, and return of conditioned fear. An emerging area of interest as it relates to impaired fear learning as a central feature of PTSD is the heterogeneity that exists in the expression and extinction of learned fears. Traditional studies of psychiatric populations recruit a group of interest (*e.g.*, traumatized veterans or civilians) and compare their results with that of an appropriate control sample at the group level or through a between-groups comparison of averaged data. Consistent with initiatives toward individualized medicine, there are efforts underway to further explore individual differences and potential subclasses of responders in clinical science. For example, the employment of statistical techniques such as latent growth mixture modeling (LGMM) allows investigators to determine underlying subclasses based on a specific variable of interest. This approach has recently been employed in the study of fear-related behaviors at the clinical level as well as conditioned fear responses derived from the laboratory (Galatzer-Levy, 2015; Galatzer-Levy et al., 2017, 2013). For example, individuals who have been traumatized and/or diagnosed with PTSD have predictably shown delayed, slower, or even non-existent rates of fear extinction when compared to non-traumatized populations (Galatzer-Levy et al., 2013).

The study of human fear acquisition and extinction remains clinically relevant for a number of reasons based on an extensive body of literature spanning the past five decades. As previously discussed, one

of the most effective psychotherapeutic interventions for PTSD and other trauma- and stressor-related disorders is PE (Foa and McLean, 2016). This strategy seeks to help individuals establish a dominant extinction memory trace, in which trauma-related cues signal safety rather than harm through graduated exposure to fear-provoking CS or triggers. The learning mechanisms underlying PE can be recruited through laboratory extinction learning and, as such, allow researchers to identify intermediate phenotypes underlying fear-related psychopathologies (Norrholm et al., 2014). One such phenotype is termed fear load, or the amount of conditioned fear exhibited during early extinction, which has shown to be prognostic of intrusive symptoms (Norrholm et al., 2014). Additionally, supplementary factors can be considered when clinicians administer exposure-based treatments, as research suggests that factors such as time of day, cognitive resources, and menstrual phase can influence fear extinction profiles (Glover et al., 2012, 2015; Milad et al., 2006a).

In addition to research aimed at improving clinical population treatment outcomes, it may also be worth investigating the potential cost of repeated trauma exposure in non-clinical populations (Levy-Gigi and Richter-Levin, 2014). Identifying individuals who are at risk for fear learning deficits following trauma exposure, regardless of clinical status, could be helpful for preventing said deficits. For example, introducing contextual-cue processing skills before trauma exposure could reduce the advancement of fear learning deficits in individuals with high-risk occupations.

In summary, it is increasingly vital to consider the literature that supports psychophysiological measures as valid tools to predict clinical risk factors and treatment outcomes for PTSD and trauma and stress-related disorders. Although PTSD is not defined as a fear-centric or fear-conditioning disorder, fear learning mechanisms are a fundamental component of this and related disorders. Notably, assessments of fear learning and extinction have introduced new discoveries about the behavioral, cognitive, and neurobiological underpinnings of trauma's psychophysiological effects. Evaluating fear extinction learning, variability, and retention may serve a critical role in the future of improving individualized treatment efficacy for trauma-related disorders and predicting clinical pathology or resilience.

4.2. Mechanisms of action of existing treatments for PTSD and development of novel therapeutic strategies for PTSD

4.2.1. Current treatments for PTSD

Pharmacological treatments for PTSD, including antidepressants and antihypertensives, were originally developed for other disorders and only later tested clinically for PTSD (reviewed in Bernardy and Friedman, 2017). While they provide a certain degree of improvement of PTSD symptoms, these treatments fail to cure the specific neurobiological deficits characteristic of PTSD. In the 1980s, clinical trials supported the use of tricyclics (TCAs) and monoamine oxidase inhibitor (MAOI) antidepressants (Davidson, 2015) but with the advent of the selective serotonin re-uptake inhibitors (SSRIs), the latter medications became more commonly used as first-line PTSD treatments. Since then, paroxetine and sertraline are the only FDA approved medications for PTSD (reviewed in Bernardy and Friedman, 2017; Locci and Pinna, 2017). Subsequent clinical trials assessed the SNRI venlafaxine to be beneficial in treating PTSD symptoms (Watts et al., 2013), with one trial in particular finding venlafaxine highly effective compared to SSRIs (Lee et al., 2016). Nefazodone is another treatment option; however, side effects are more prominent and include the risk of liver failure (Baldwin et al., 2014; Hoskins et al., 2015; Lee et al., 2016).

It is not uncommon, unfortunately, for pharmacological treatment to fail at improving patients' symptoms. First line trauma-focused psychotherapy, including PE, is helpful when a pharmacological treatment fails, and is considered the rule rather than the exception. Indeed, only about half of patients respond to SSRIs and more than a third of SSRI-treated patients fail to respond, do not reach full remission, or even develop SSRI resistance (Bernardy and Friedman, 2015; Golden et al., 2002; Kemp et al., 2008; Rush et al., 2006). Furthermore, most patients who initially respond to SSRI treatment fail to maintain therapeutic gains over time. In particular, veterans affected by PTSD are generally resistant to SSRI therapy (Friedman et al., 2007; Prigerson et al., 2001; Schnurr et al., 2007). Similarly, general abuse – but especially abuse and neglect at a young age – predicts a lower response to SSRIs (Williams et al., 2016). Treatment becomes even harder when chronic PTSD patients present with comorbid mood disorders, such as major depressive disorder and drug abuse; ultimately, these people are less likely to be successfully treated (Friedman et al., 2007; Kessler et al., 2017).

For those who fail to achieve complete remission from PTSD following pharmacotherapy, PE in combination with an SSRI can be the best option rather than receiving adjunctive medication. PTSD patients related to World Trade Center attack who received paroxetine in combination with PE showed greater improvement compared to individuals who received PE alone (Schneier et al., 2012). Among adjunct pharmacological treatments adopted to enhance cognitive-behavioral therapy, DCS and hydrocortisone are some of the most common to be used for PTSD. Several studies have failed to find improvement with DCS, however, while hydrocortisone, which was evaluated to enhance PE, was found to be beneficial in veterans with PTSD (de Kleine et al., 2012; Hofmann et al., 2015; Litz et al., 2012; Rothbaum et al., 2014).

As sleep disturbances are common in PTSD patients and can worsen perceived levels of stress, depression, and suicidal thoughts, they are often a focus of treatment. Trazodone and prazosin are widely used treatments for PTSD. The alpha-1 adrenergic receptor antagonist prazosin and the alpha-1 adrenergic receptor antagonist and 5-HT2 receptor antagonist trazodone are being used to treat sleep disturbances in PTSD (Thomas, 2014). However, the beneficial effects of prazosin on sleep disturbances are not clear (McCall et al., 2018).

Collectively, current pharmacotherapy for PTSD relies mostly on fluoxetine, paroxetine, sertraline and venlafaxine alone or in combination with PE. The beneficial therapeutic gains are modest with all of these, (Bernardy and Friedman, 2015; Locci and Pinna, 2017), hence, the development of new agents that act through different mechanisms (rather than inhibition of serotonin reuptake) or new therapeutic strategies that can help treatment-resistant patients, is needed. This also suggests the need to develop biomarker-based therapy designed for specific trauma-exposed individuals who develop PTSD and fail to respond to traditional treatments (Pinna and Izumi, 2018). Undisputable progress has been made to assess the validity of biomarkers for psychiatric disorders, although, the field still remains underdeveloped compared to other fields of neuroscience (Fernandes et al., 2017). Investigation toward discovering potential novel biomarkers to guide precision medicine for the treatment of PTSD, and thereby, prompting the development of novel and specific treatments and increasing the success of clinical trials, is thus required.

Recent advances in the field suggest biomarker-based treatments for PTSD may not be a far reach (discussed in Aspesi and Pinna, 2018). Employing more sophisticated methodological tools and the search for valid animal models, has also become essential to reliably correlate behavioral changes of the disorder with neurochemical alterations (reviewed in Ngounou Wetie et al., 2013). The overlap of symptoms and the comorbidity with other psychiatric disorders, and even with suicidal ideation and drug abuse disorder, suggest a biosignature for PTSD should include a set of biomarkers rather than just a few (Locci and Pinna, 2017). A refined approach to more specifically and unambiguously "biodefine" PTSD might be one of establishing a *biomarker axis;* or in other words, assessing the interrelation of various biomarkers, which fluctuate in concert and correlate with behavioral modifications, will reveal a more nuanced description. Insofar, a *biomarker axis* may provide a higher accuracy in the diagnosis of the disorder with benefits for prediction in PTSD treatment response and relapse (discussed in Locci et al., 2018; Pinna and Izumi, 2018). Progress

in assessing predictors of PTSD development and treatment response and biomarkers for the unique neurobiology of PTSD will guide the future of novel PTSD medications designed to act on a range of GABAergic, glutamatergic, adrenergic, neuroendocrinologic, as well as inflammatory targets.

4.2.2. Unveiling new biomarkers and treatment options for PTSD

SSRIs are the most widely used agents to treat PTSD. They act through a number of recently characterized molecular mechanisms rather than just by inhibiting serotonin reuptake (Pinna, 2015). Examples of other mechanisms include the stimulation of the progesterone metabolite, allopregnanolone biosynthesis and of neurotrophic factors, such as BDNF. Both allopregnanolone concentrations and BDNF expression are found deficient in PTSD (reviewed in Nin et al., 2011). These findings not only have contributed to our understanding of PTSD neurobiology but they also stimulated the development of novel, targeted treatment options and improved therapeutic strategies. In this respect, impairment of neuroactive steroid concentrations and behavioral abnormalities in neuropsychiatric disorders, including PTSD and major depression has been extensively studied.

As outlined below, the positive GABAergic modulator allopregnanolone and its equipotent isomer, pregnanolone, have been of special interest. In rodent models, a reduction of corticolimbic allopregnanolone levels by prolonged social isolation or exposure to single prolonged stress, two putative rodent models of PTSD (Aspesi and Pinna, 2019), resulted in development of anxiety-like behavior, aggression and

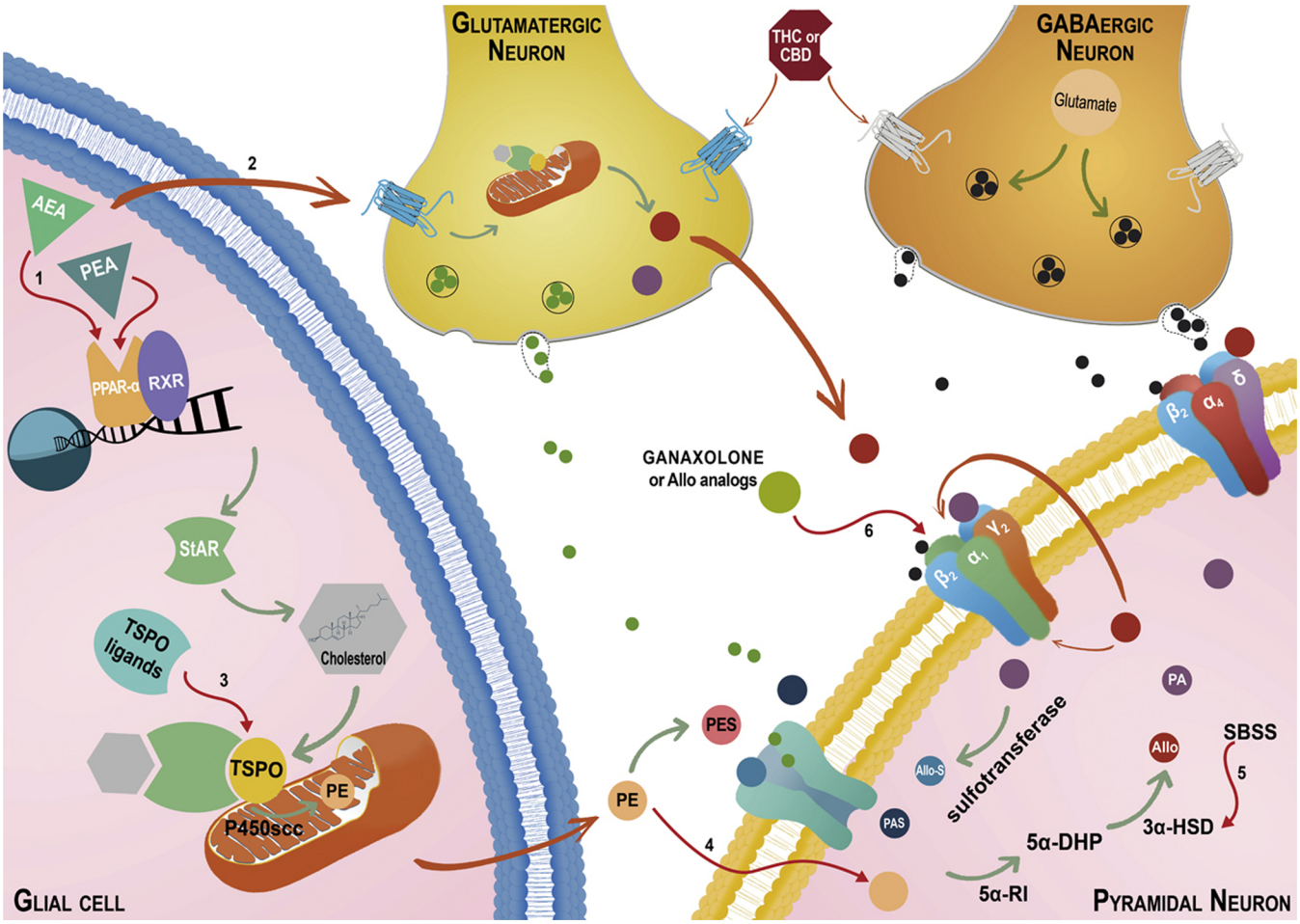

Fig. 6. Novel treatment strategies to regulate emotional behavior. Allopregnanolone (Allo) and its equipotent stereoisomer pregnanolone (PA) are synthesized in glutamatergic corticolimbic pyramidal neurons and after their secretion, they act as positive allosteric modulators of the action of GABA at $GABA_A$ receptors located on cell bodies or dendrites of pyramidal neurons (Agis-Balboa et al., 2007, 2006; Pinna et al., 2000). Allopregnanolone's neurophysiological role in regulating the fine-tuning of $GABA_A$ receptors is involved in the regulation of emotional behavior (Pinna and Izumi, 2018; Pinna et al., 2000). Sulphotransferase converts allopregnanolone and pregnanolone into allopregnanolone sulfate (Allo-S) and pregnanolone sulfate (PAS). Pregnanolone sulfate inhibits NMDA receptors, which has relevance for neuroprotection (Vyklicky et al., 2016) and may play a role in the regulation of cognition and emotional behavior (reviewed in Locci and Pinna, 2017). Depicted are several strategies to improve PTSD symptoms by increasing corticolimbic allopregnanolone levels or by directly activating $GABA_A$ receptors. 1. The intracellular peroxisome proliferator-activated receptor (PPAR-α), a cannabinoid target heterodimerize with the retinoid X receptor (RXR) and initiates transcription. Given that endocannabinoids activate PPAR-α, the activation of these nuclear receptors represents a novel mechanism by which cannabinoids and ethanolamides may modulate behavior. The ethanolamide, N-palmitoylethanolamine (PEA) is a PPAR-α endogenous agonist, which is decreased in PTSD patients (Wilker et al., 2016). Recent preclinical findings showed that supplementing PEA in rodent PTSD models improves emotional behavior by enhancing allopregnanolone biosynthesis in corticolimbic glutamatergic neurons (Pinna and Izumi, 2018). 2. Agonist for the CB1 receptor may also improve behavior by activating pregnanolone biosynthesis (Vallée, 2016; Vallée et al., 2014). 3. TSPO ligands may induce an *upstream* stimulation of neurosteroidogenesis by enhancing the entry of cholesterol into the inner mitochondrial membranes of glial cells, and stimulating its conversion into pregnanolone. Pregnanolone is then taken up by glutamatergic neurons and increase downstream allopregnanolone levels. 4. Pregnanolone can also be sulfated to pregnanolone sulfate and act at NMDA receptor. 5. Low doses of SSRIs induces a *downstream* activation of allopregnanolone concentrations by acting at 3α-HSD. 6. Administration of allopregnanolone or allopregnanolone's analogs (*e.g.*, ganaxolone) by directly activating $GABA_A$ receptors may also improve PTSD and other psychiatric disorders characterized by impaired neurosteroidogenesis. Modified from Pinna (2018).

enhanced contextual fear conditioning responses (Dong et al., 2001; Pibiri et al., 2008; Pinna and Rasmusson, 2014; Zhang et al., 2014b). Similar associations have been found in humans: a reduction in the concentration of allopregnanolone and pregnanolone was observed in cerebrospinal fluid (CSF) and serum of unipolar depression and PTSD patients (Pineles et al., 2018; Rasmusson et al., 2006; Schüle, 2014; Uzunova et al., 1998). In particular, Rasmusson and colleagues showed that a marked decrease in the CSF and blood levels of allopregnanolone and pregnanolone in women negatively correlated with PTSD re-experiencing and comorbid depression (Pineles et al., 2018; Rasmusson et al., 2006). A negative correlation between CSF allopregnanolone concentrations and PTSD total CAPS was more recently confirmed in male patients (Rasmusson et al., 2016). Likewise, patients affected by depression showed downregulation of allopregnanolone biosynthesis in serum, plasma, CSF, and prefrontal cortex Brodmann's Area 9 (Agís-Balboa et al., 2014; Romeo et al., 1998; Uzunova et al., 1998; Van Broeckhoven and Verkes, 2003) (reviewed in Locci and Pinna, 2017; Pinna, 2014). In support, a number of clinical investigations underlie the relevance of allopregnanolone biosynthesis as a biomarker of affective disorders, as reported by observations demonstrating decreased downregulation of allopregnanolone concentrations in postpartum depression (Nemeroff, 2008); following treatment with finasteride, an agent that inhibits allopregnanolone biosynthetic enzymes (Altomare and Capella, 2002; Welk et al., 2017); and in patients with anorexia nervosa or obesity affected by anxiety spectrum disorders and depressive symptoms (Dichtel et al., 2017). In this respect, it is intriguing that administering SSRIs upregulates serum, plasma, CSF, and brain allopregnanolone concentrations in association with remission of behavioral symptoms (Agís-Balboa et al., 2014; Romeo et al., 1998; Uzunova et al., 1998).

The normalization of allopregnanolone concentrations must certainly be included in the multiple mechanisms of action for the antidepressant and anxiolytic effects of SSRIs (Pinna, 2015). Furthermore, preclinical studies are in support of allopregnanolone biosynthesis and its interaction with $GABA_A$ receptor subtypes as a *biomarker* candidate for stress-induced behavioral abnormalities, which include inappropriate and exaggerated fear responses and impaired fear extinction, which are a core feature of PTSD neurobiology (Pibiri et al., 2008; Pinna and Izumi, 2018; Pinna and Rasmusson, 2014). This evidence also suggests new treatments that counteract the stress-induced downregulation of neurosteroid concentrations may improve symptoms of PTSD. Several neuronal targets to enhance steroidogenesis have recently been discovered and offer promising therapeutic approaches to improve emotional symptoms by increasing neurosteroid levels and modulating neurotransmitter systems (Aspesi and Pinna, 2019) (summarized in Fig. 6). Assessing subpopulations of PTSD patients for downregulation of allopregnanolone biosynthesis, and subsequently treating those patients with neurosteroidogenic agents, such as drugs that act at the translocator protein (TSPO) receptor or the endocannabinoid system, or with allopregnanolone mimetics could be a new form of precision medicine. Intriguingly, recent phase 3 clinical trials demonstrated a fast remission of post-partum depression in 70% of patients after a two-day course of intravenous allopregnanolone (Kanes et al., 2017; Locci and Pinna, 2019). These results have led to the FDA approval of allopregnanolone for postpartum depression on March 2019.

The description that follows on neuronal targets that are currently explored for the development of novel treatments for PTSD, ties back into allopregnanolone biosynthesis.

4.2.3. Endocannabinoids, CB1 and PPAR-α agonists

The therapeutic relevance of cannabinoids for PTSD has been the focus of several debates. Cannabis is often used as a self-medication by patients (Bernardy and Friedman, 2015; Bonn-Miller et al., 2014; Cougle et al., 2011; Earleywine and Bolles, 2014), which is primarily composed of THC and cannabidiol (CBD) (Bergamaschi et al., 2011; Budney et al., 2004). This is likely facilitated by a greater cannabinoid receptor density in patients with PTSD (Neumeister et al., 2013). Most studies on the effects of cannabinoids on fear memory have focused on increasing fear extinction by targeting CB1. Stern et al. (2015) found CBD administered immediately after memory retrieval disrupted consolidated fear memories, and persisted for 22 days after application. Administration of THC and THC + CBD resulted in a similar effect (Stern et al., 2015). These data are in support of a role for CBD and THC on modulation of fear in PTSD by facilitating extinction learning through a reconsolidation blockade. CBD may also decrease anxiety and anhedonia and THC may reduce nightmares and insomnia in PTSD (reviewed in Loflin et al., 2017). Two randomized controlled clinical trials of THC, CBD, and the combination of THC + CBD to assess efficacy to treat PTSD are ongoing (*e.g.*, NCT02759185 and NCT02517424).

Recent evidence also suggests that the endocannabinoid and the neurosteroid systems are inter-related. Evidence shows both allopregnanolone and the endocannabinoid, anandamide (AEA) levels are low in depression and PTSD and in animal models of anxiety and depression (Hill et al., 2013, 2008; Rasmusson et al., 2006; Romeo et al., 1998; Uzunova et al., 1998). Moreover, CB1 is highly expressed in neurons where enzymes for neurosteroidogenesis are also present, and in brain areas that regulate fear responses, such as hippocampus and amygdala (Katona, 2009). Of note, THC induces a 30-fold increase of the allopregnanolone's precursor, pregnanolone by acting on CB1 (Vallée, 2016; Vallée et al., 2014). Thus, the endocannabinoid system may be a novel pharmacological target to elevate allopregnanolone biosynthesis and facilitate fear extinction in PTSD patients.

Another endocannabinoid target that has recently been examined for its ability to induce allopregnanolone biosynthesis is the peroxisome proliferator-activated receptor (PPAR)-α class of nuclear hormone receptor, which is involved in several cellular and molecular mechanisms regulating neuroinflammation (Pinna, 2018). The endocannabinoid, palmitoylethanolamide (PEA) induce potent antidepressant effects by acting at PPAR-α (Yu et al., 2011) and recent studies have demonstrated PEA increases allopregnanolone levels in the spinal cord and brain stem. More importantly, PEA-induced increase of allopregnanolone in the hippocampus and amygdala was associated with faster fear extinction learning and improvement of aggression in socially-isolated mice (Locci et al., 2017; Locci and Pinna, 2017; Sasso et al., 2012). These findings highlight a fine network that coordinates the neurosteroid and the endocannabinoid systems. Hence, novel cannabinoid-like agents with neurosteroidogenic properties but devoid of psychotomimetic effects could be beneficial pharmacological therapies for PTSD patients.

4.2.4. Translocator protein (TSPO) agonists

TSPO is located on the outer mitochondrial membrane and plays an important role in cholesterol transport onto the inner mitochondrial membrane (depicted in Fig. 6). Stimulation of the TSPO receptor results in a downstream increase of allopregnanolone levels. In mouse models of PTSD, TSPO ligands (AC-5216/XBD173 and etifoxine) potently increase allopregnanolone levels in the hippocampus and cortex and improve anxiolytic-like behavior (Kita et al., 2004). Intriguingly, these findings have been demonstrated also in studies conducted in anxious patients (Rupprecht et al., 2010; Rupprecht et al., 2009; Schüle, 2014). AC-5216/XBD173 and YL-IPA08 also improve PTSD-like behavior in rodent studies of situational reminders and contextual fear responses (Qiu et al., 2013). Chronic administration with YA-IPA08 markedly reduced anxiety-like behavior and contextual fear responses in mice exposed to single-prolonged stress, an effect that was inhibited by the TSPO antagonist, PK11195 (Zhang et al., 2016, 2014b). Behavioral improvements induced by YA-IPA08 were positively correlated with increased serum and cortical allopregnanolone levels (Zhang et al., 2014b). The evidence thus far suggests that TSPO agonists could be future therapeutic agents for PTSD, and should be further explored for this potential.

4.2.5. Selective brain steroidogenic stimulants (SBSSs)

A strategy to facilitate fear extinction deficits in PTSD patients might be offered by administering low doses of SSRI antidepressants (see Fig. 6). Laboratories have shown that *low doses* of SSRIs (*i.e.*, 1/10 of the doses that inhibit 5-HT reuptake), which fail to affect serotonergic mechanisms, normalize allopregnanolone levels and improve PTSD-like behavior in allopregnanolone-deficient mice (Pinna, 2013, 2004) by acting as *selective brain steroidogenic stimulants (SBSSs)* (Pinna et al., 2006). SSRIs are associated with high non-response rates in the treatment of PTSD patients at doses that engage serotonergic mechanisms (reviewed in Pinna, 2015). Hence, one may wonder whether a low dosage of an SSRI may be more effective in PTSD treatment. Clinical trials should be conducted to establish whether SSRI at low neurosteroidogenic doses offer a pharmacological advantage over SSRI doses that are currently prescribed in the treatment of PTSD and depression. SBSSs may provide benefits in selected subpopulations as adjunct treatment in trauma-focused therapy for PTSD (*e.g.*, PE or CTP). Interestingly, findings from Dr. Lovick support the use of low neurosteroidogenic doses of fluoxetine to improve premenstrual syndrome, a disorder characterized by a rapid drop of neuroactive steroid levels (Lovick, 2013).

4.2.6. Allopregnanolone analogs

Administration of allopregnanolone or its analog, ganaxolone, improves behavioral dysfunction related to corticolimbic allopregnanolone deficits (Pinna and Rasmusson, 2014). Ganaxolone, administered immediately after reactivation, facilitated fear extinction and, more importantly, enhanced fear extinction retention at recall, suggesting a long-lasting effect (Pinna and Rasmusson, 2014). Ganaxolone also showed anxiolytic and antiaggressive effects (Locci et al., 2017). Other synthetic neurosteroid analogs, BR351 or BR297 reduces aggressive behavior and their effects on fear extinction are currently being examined (Locci et al., 2017).

4.2.7. Precursors of allopregnanolone and sulfated congeners

Administration of the allopregnanolone precursor pregnanolone reduced neuronal activity in brain regions associated with generation of negative emotions in response to emotional stimuli (Sripada et al., 2013). Hence, administering directly allopregnanolone or its precursors may be valuable treatment options to improve efficacy of exposure-based cognitive treatments for PTSD (Fig. 6).

Sulfated neurosteroids are currently the focus of interesting treatment developments in neuropsychopharmacology. The inhibitory role of pregnanolone sulfate (PAS) on NMDA receptors has just recently been discovered (depicted in Fig. 6). PAS is specifically potent at inhibiting tonic rather than synaptically activated NMDA receptors (Vyklicky et al., 2016). Activation of synaptic NMDA receptors is important for neurophysiological processes, including synaptic plasticity, learning and memory, and synaptogenesis, while *tonic* NMDA receptor activation results in excitotoxicity. This mechanism is relevant for developing a novel class of steroid-based NMDA-inhibitors as therapeutics with the benefit of being devoid of ketamine-like psychotomimetic side effects. Several PAS analogs have recently been developed (Adla et al., 2016) that show no activity at synaptic NMDA receptors but are highly selective on tonic-activated receptors (Vyklicky et al., 2016). Collectively, neurosteroids that potentiate GABAergic neurotransmission and their sulfated derivatives that inhibit tonic NMDA receptor neurotransmission may work in concert to improve cognitive and emotional deficits in PTSD patients.

4.3. The role of subjective experience in fear

Fear is a common human emotion. As is true for all emotions, fear is a private experience that cannot be observed directly. Scientific studies of such inner experiences typically require some form of self-reporting. People can only provide a verbal report of information if it is processed consciously. We argue here that subjective reports of fear (and other emotions) are not unreliable proxy measures of emotions, as suggested by some theorists. Rather, they are the best direct, and, so far, the only easily accessible measures of emotions. In fact, verbal self-report remains the gold standard in studies of consciousness and emotions, including fear.

Because non-verbal reporting is the only option in non-verbal (non-human) organisms, determining whether other animals have conscious, subjective experiences is difficult to ascertain. While other methods of measurements that do not require verbal report may exist, these also depend on introspection. As we discussed elsewhere (LeDoux and Hofmann, 2018), we argue here that use of the term “fear” (as well as other emotion words) should be restricted to subjective experiences in order to eliminate much of the conceptual confusion when discussing emotions. We recommend that future research examine the relationship between subjective report, behaviors, and physiological responses of fear and anxiety in order to explain the reasons for the dissociation that has been reported in the literature between these measures.

The theoretical framework to incorporate consciousness and emotions is provided in the high-order theory of emotions (LeDoux and Brown, 2017), which builds on recent developments in the science and philosophy of consciousness, arguing that a general network of cognitions underlies both cognitive and emotional states of consciousness. What distinguishes cognitive and emotional states of consciousness, and different kinds of emotional states in higher-order emotion theory is the kind of inputs processed. The subcortical circuit is the defensive survival circuit that detects and responds to threats. The consequences of defensive survival circuit activation (such as brain arousal, body feedback, *etc.*) contribute indirectly to the experience of fear but do not determine it (LeDoux and Pine, 2016).

Fear is then the product of the cognitive assessment that we are in harm's way, a view that allows fear to arise from activity in any survival circuits (fear of being harmed by starvation, dehydration, hypothermia, reproductive isolation, and so forth), or by existential concerns (such as fear of the eventuality of death or the meaninglessness of your life), in addition to predatory-related dangers that trigger the defensive survival circuit (LeDoux, 2015a; LeDoux and Pine, 2016).

We believe that the clinical relevance is evident. The primary reason why people seek the help of mental health specialists is because they feel bad and want to feel better. A treatment that reduces behavior (avoidance) and physiological responses (hyperarousal) but does not diminish subjectively reported fearful feelings is not likely to be viewed as a satisfactory outcome by the suffering person.

In the contemporary treatment literature, self-reports, and the subjective experiences that these reports reflect, have not been given much credence. This may reflect the influence of behaviorism in the development of both traditional behavioral therapy and cognitive behavioral therapy, as well as findings suggesting that behavioral physiological responses related to fear and other emotions in humans are poorly correlated (Hodgson and Rachman, 1974; Lang, 1968; Rachman and Hodgson, 1974).

Today, most therapists routinely use subjective patient report as part of treatment. Although the reduction in reported fear ratings during an exposure session is, in fact, an important factor that determines the success of treatment (*e.g.*, Hofmann, 2014), the value of self-report measures continues to be debated. We conclude that self-report assessments of fear are crucially important for measuring this human emotion.

4.4. Role of the cholinergic system in PTSD; potential of miRNA as therapeutic strategy

Fear is an integral part of human life, ranging from day-to-day anxiety experienced by each parent to international terror bursts with increasing incidence and spread. The strong bodily sensation of fear, sensed by each of us to varying degrees, raises questions regarding the

underlying molecular changes induced by such an intense reaction, as well as the regulators of long-term fear-inducible physical and mental consequences, and the interactions between them. These questions may be addressed by combining molecular (Meydan et al., 2016) and neurocognitive (Arzy et al., 2009, 2011; Craig, 2002) approaches and subjecting the findings to advanced analyses that are aimed at assessing the impact of these risks on human health and wellbeing (Peer et al., 2017; Soreq, 2015). For instance, a population-based analysis was used to investigate the consequences of the repeated exposure of the Israeli population to chronic terror-related stress. It was found that consistent exposure to terror threats ignites combined annual increases in pulse rate and in the inflammatory biomarker C-reactive protein, indicating acquired neuro-immune risks of all-cause mortality (Shenhar-Tsarfaty et al., 2014).

The intense physiological reaction induced by fear immediately impacts bodily and nervous circuits through sympathetic and dopaminergic activation. Fear and stress are therefore known to facilitate the emergence of major neuropsychiatric disorders, such as schizophrenia. The relationships between environmental, bodily and neurocognitive mechanisms have been well established (Blanke, 2012; Craig, 2002). However, how these relationships are translated to the underlying molecular level remain unclear. Several candidates are gaining tractions, though: for instance, at the genomic level, there is evidence for the putative involvement of microRNA (miR) regulators (Bartel, 2009) in both neuronal and immune processes (Soreq and Wolf, 2011). The small and effective miR molecules may lead to rapid, yet reversible, changes in stress-inducible pathways (Fig. 7). Application of lentivirus-mediated suppression of acetylcholinesterase (AChE) clearly revealed both cognitive and metabolic implications of the stress-induced AChE-targeting miR-132. Importantly, miR-132 is evolutionarily conserved, and interactions of miR-132 and AChE are causally involved in minimizing the cognitive damages induced by acute stress events (Shaltiel et al., 2013). Recent clinical reports of dementia following chronic use of cholinergic suppressors (such as pharmaceutical blockers of muscarinic receptors to control incontinence) provide further support for a critical role of cholinergic function in fear and age-related neurodegenerative conditions (Weinstein et al., 2018). In peripheral tissues, the stress-accompanying impact of miR-132 elevation extends to hepatic

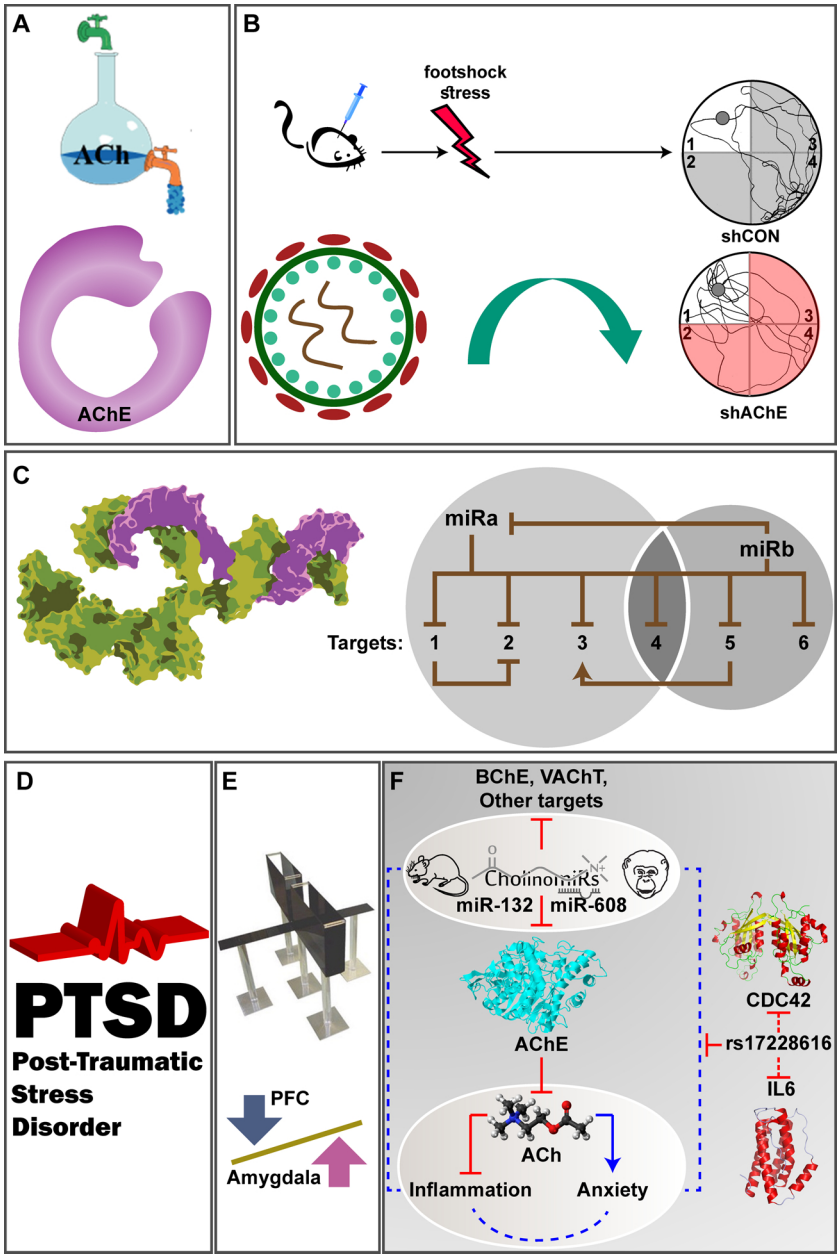

Fig. 7. Personalized aspects of cholinergic fear reactions in mouse and human brain analyses. (A) Imbalanced acetylcholine (ACh) levels lead to excessive fear reactions (hyper-activated cholinergic signaling) or cognitive injury (prolonged suppression). Acetylcholinesterase (AChE) degrades ACh, serving as the balancing enzyme (Soreq, 2015). (B) Following foot-shock stress, mice fail to locate a hidden platform in the Morris Water Maze test (Shaltiel et al., 2013). Intracerebrally injection of a viral suppressor of AChE (shAChE) leads to activation of cholinergic signaling and improves navigation of stressed mice to the platform as compared to mice injected with a control virus (shCON) (Shaltiel et al., 2013). (C) Small microRNA (miR) regulators of cholinergic gene expression wrap around their target gene products, block protein expression and consequently the signaling balance. miRs may each interact with many targets. Each target may be controlled by many miRs. (D) Humans under long-term fear of terror show impaired cardiac functioning and several PTSD symptoms (Shenhar-Tsarfaty et al., 2015). (E) Mice under fear prefer the enclosed over the more anxiety-provoking open arms of the elevated maze (top). In humans with PTSD, hyper-activated amygdala and suppressed pre-frontal cortex (PFC) functioning is observed in functional MRI (fMRI) (bottom). (F) Human carriers of a single nucleotide polymorphism (SNP) in the AChE gene's miR-608 binding site show a hyper-activated PFC, an interrupted amygdala response, and no post-stress symptoms (Lin et al., 2016), whereas humans with a SNP in the primate-specific miR-608 gene show reduced risk of sepsis following head injury (Zhang et al., 2015). Cholinergic genes (*e.g.*, butyrylcholinesterase, BChE; vesicular ACh transferase, VAChT) and/or their miR targets may modify fear and inflammatory responses. Suppression by miR-608 of its other targets, including CDC42 and IL6 is modified in SNP carriers (Hanin et al., 2014). SNPs in the AChE binding sites of other miRs (Simchovitz et al., 2017) thus leading to complex personalized responses to fear.

lipid accumulation (Hanin et al., 2018).

At the translational level, miRs are 'druggable' entities, the impact of which may be mitigated by suppressing targeted miRs *via* intravenous injection of synthetic antisense oligonucleotides (Mishra et al., 2017). Thus, both the miR-132 related inflammation and the hepatic lipid accumulation may be reversed by administration of synthetic antisense oligonucleotides designed to be complementary to the miR sequence (Hanin et al., 2018; Shaked et al., 2009). This, in turn, suggests that anxiety- and fear-related cholinergic-regulating miRs are causally involved in mediating brain-to-body messages, affecting both mental and physiological parameters that are reversible and potentially treatable.

The apparent involvement of miRs in regulating post-trauma brain activity raises the need to validate the relevance of cholinergic signaling as a developing therapeutic strategy. Correspondingly, a single nucleotide polymorphism (SNP) disrupting interaction of the primate-specific miR-608 with the AChE gene is associated with mild elevations in trait anxiety and inflammation (Geula et al., 2014). This is accompanied by elevated blood pressure and brain AChE activities, indicating mal-responsiveness of minor allele carriers to anti-AChE agent (Hanin et al., 2018). However, carriers of the minor allele also show elevation in prefrontal activity under stress, as measured by fMRI, suggesting that they may avoid post-traumatic stress symptoms (Lin et al., 2016). This highlights a possibility for other therapeutic options when attempting to re-script traumatic memories with repeated exposure therapy (Grunert et al., 2007), considering that a number of variables might mediate the therapeutic effect of re-scripting- and/or exposure-based therapies. Imbalanced miR-608 activities are yet more drastically evident under inherited disruption of miR-608 by a SNP in the miR itself. This genomic change is associated with an increased risk of sepsis following head injury (Zhang et al., 2015), indicating a collapse of inflammatory regulation in minor allele carriers.

Considering the miR-regulated alterations following trauma, the timeline aspects of fear-induced symptoms are of special interest, since depression, for example, is known to associate with both immune malfunctioning and a worsened course of diverse aging-related diseases. This raises the possibility that during the post-reproductive and evolutionarily "blind" years, chronic exposure to trauma may shorten one's life span, compatible with the antagonistic pleiotropy hypothesis (Wiilliams, 1957). Supporting this notion, depression, inflammation and cholinesterase activities all increase with aging (Shenhar-Tsarfaty et al., 2016). Moreover, metabolic syndrome patients with higher risk to develop diabetes show increased circulating cholinesterase levels and pulse values, and diabetic patients present simultaneous increases in depression, inflammation and circulation cholinesterase activities, suggesting that cholinergic impairment precedes depression. Taken together, these findings indicate that a malfunctioning cholinergic regulation weakens the otherwise protective link between depression and the pathogen–host defense, with global implications for aging-related diseases.

Functional neuroimaging enables detection of processes that may reflect the above-mentioned molecular processes. In the framework of personalized neuropsychiatry, several main approaches should be taken into consideration: task-related fMRI, resting-state fMRI, MR-spectroscopy and molecular neuroimaging. Task-related fMRI is well known in the evaluation of cognitive function. A recently introduced approach has combined virtual reality techniques into the fMRI-theater in order to detect bodily-signals such as heart and respiratory rates (Allard et al., 2017; Ronchi et al., 2017). These signals were mostly activating the insular cortex and limbic system, in probable relation to their role in reflecting emotional processes (Allard et al., 2017; Ronchi et al., 2017). While task-related fMRI in general and VR-based specifically are lengthy, labor intensive and require specialized settings, resting-state fMRI has proven in the recent years to be easily applicable in a 5–10 min recording session. Moreover, new computational tools enable to extract brain-networks (such as memory, emotion, or attention networks) and quantify their properties in both the gray (Yeo et al., 2011) and the white (Peer et al., 2017) matter.

In the framework of neuropsychiatry, special importance should be assigned to the DMN. The DMN comprises a set of brain regions which process self-referential cognitive operations such as elaboration on autobiographical memories, simulation of future occurrences or mind wandering (Buckner et al., 2008; Raichle et al., 2001). As such, the DMN has been implicated in several neuropsychiatric disorders (Zhang and Rachle, 2010). Using resting-state fMRI, we were recently able to demonstrate in patients with conversive paralysis, a stress-induced self-related activity in the DMN that leads to an escalating cascade of events in emotional, memory and body-processing networks, ending in alterations of the sensorimotor network (Monsa et al., unpublished observations). This cascade of events demonstrates how stress-induced hyperactivity in the DMN leads, through neurocognitive operations, to the clinical neurological bodily manifestation of paralysis. However, integrating the molecular and large-scale neuro-circuit levels together is still highly challenging. Several studies used MR-spectroscopy to show elevation of N-acetyl-aspartate as well as choline activity in such circuits (Nacewicz et al., 1993). The nascent field of molecular MR imaging may shed a new light on the interaction between neuro-cognition, brain circuitry, and the molecular pathways involved.

While both neuro-genomics and neuro-cognitive studies of fear-related mechanisms of action have made major progress over the past decade, major challenges lie ahead in the need to combine approaches from different levels of the neurosciences – from molecular and cellular levels to large-scale networks – into an integrative entity. Inter-individual variability, small group sizes and sampling difficulties all contribute to these difficulties; nevertheless, a recent brain mapping study shows early deterioration of cholinergic pathways in patients with Alzheimer's disease (Schmitz et al., 2016), a condition associated with behavioral alterations that include increased fear, and isolation of exosomes enables quantification of microRNAs in plasma samples, indicating that progress will soon be made also in these challenging bridging efforts. As is often the case, breakthroughs depend on convergent efforts that combine seemingly distinct fields of research into a single entity.

4.5. Role of alterations in the perisynaptic environment in fear learning and memory; identification of potential therapeutic targets

Synaptic adaptations of the brain in response to chronic stress have consistently been demonstrated in animal models (McEwen et al., 2016). Brain regions that are particularly involved include the hippocampus, amygdala and prefrontal cortex (Miller and McEwen, 2006). An overview of the animal models thought to model aspects of PTSD is beyond the scope of this review, but include stressors such as footshock, underwater trauma and social defeat (Schoner et al., 2017). A recent study in rats that investigated the effects of underwater trauma on activity patterns in limbic regions found not only that patterns differ between specific limbic (sub)regions, but also depend on the behavioral phenotype that develops after trauma-induction (classified as anxious, anhedonic or not-affected) (Ritov et al., 2016). Although technical limitations prevent such detailed assessments in humans suffering from PTSD, loss of hippocampal, amygdalar and anterior cingulate cortical gray matter volume has been identified in PTSD patients and animal models alike (Bennett et al., 2016; Meng et al., 2016). Of note, one study that examined dendritic spines in PTSD-patients reported increased numbers of immature dendritic spines in the ventral medial frontal cortex (Young et al., 2015). Thus, while the expectation that synaptic abnormalities are implicated in clinical PTSD is mostly based on findings from animal models, clinical findings in PTSD-patients appear to suggest a similar underlying neuropathology and imply abnormalities in the (peri)synaptic environment.

Current pharmacotherapies for PTSD may work in part through their action on synaptic connectivity. Antidepressants most commonly

prescribed for treating PTSD raise the levels of BDNF and enhance signaling through CREB whilst promoting synaptic growth and neurogenesis (Carlezon et al., 2005; Duman, 2004). The actions of the antidepressant ketamine on synapse formation (Li et al., 2010) are particularly interesting because, in contrast to other antidepressants, ketamine functions very rapidly. The therapeutic effects of ketamine were recently found to depend on early- and sustained activation of AMPA receptors (AMPARs) (Zanos et al., 2016). This finding is in line with the observation that surface diffusion of AMPARs is required for both long-term potentiation (LTP) as well as contextual learning (Penn et al., 2017). AMPAR surface diffusion can readily be affected through protein-protein interactions, and this mechanism was thus suggested as a possible target for the modulation of synaptic potentiation and learning (Zanos et al., 2016).

A crucial factor in fear learning and memory is the role of context. As described previously in this review, deficits in contextual processing can lead to maladaptive inflexible behavior seen in a number of psychiatric disorders, notably PTSD where out-of-context experiences appear to be at its very core (Maren et al., 2013). Hence, Contextual Fear Conditioning (CFC) in rodents – as described in Section 3.1 – is a frequently employed paradigm to study aspects of fear learning and memory that are possibly related to the neuropathology of PTSD. CFC, interestingly, has been found to affect neuronal integrity where synaptic function appears to be particularly vulnerable. For example, proteins relevant for LTP were linked to long-term memory formation after CFC (Abel et al., 1997; Scharf et al., 2002). Furthermore, synaptic protein degradation in the hippocampus was found to underlie the destabilization of retrieved fear memory (Lee et al., 2008).

Cell adhesion molecules (*e.g.*, integrins, immunoglobulin-like (Ig) adhesion molecules and cadherins) in the brain connect pre- and postsynaptic sites and may be disrupted by CFC, with serious consequences for the maintenance of inter-cell stability and the preservation of synaptic integrity. CFC was found to regulate hippocampal levels of the cell adhesion molecules NCAM and L1 (both belong to the Ig-superfamily) depending on time and stressor duration (Merino et al., 2000). NCAM can undergo a posttranslational modification that is implicated in the neural mechanisms underlying long-term memory formation, termed polysialylation (PSA), and is required for synaptic remodeling (Nothias et al., 1997). Fear conditioning using a stressful 0.4 mA stimulus increased the number of PSA-NCAM$^+$ neurons in the hippocampal dentate gyrus, whereas these numbers were reduced with a more traumatic 1 mA stimulus (Sandi et al., 2003). Furthermore, prior application of chronic restraint stress in rats facilitates subsequent CFC. These rats also displayed a reduced protein expression of NCAM in the hippocampus although protein expression of PSA-NCAM was increased (Sandi et al., 2001). The finding that CFC can be affected by a preceding stressor is in line with the observation that stressful experiences can trigger PTSD in susceptible individuals; moreover, hypercortisolemia has been found in PTSD patients (Yehuda, 2001). In agreement, glucocorticoid infusion into the hippocampus of mice was found to result in PTSD-like memory impairments, as these animals became unable to correctly identify the context as a threat predictor (Kaouane et al., 2012). In corroboration with the link between hippocampal NCAM and CFC specifically, intracerebroventricular infusion of C3d, a synthetic peptide ligand that binds the Ig-like module of NCAM, was found to attenuate the expression of CFC when administered few hours post-training (Cambon et al., 2003). The evidence that the effects of a pre-existing stressor on CFC may be mediated through altered expression of cell adhesion molecules and/or their posttranslational modifications opens up the possibility to design putative treatment strategies.

Nectins are, akin to NCAMs, Ig-like adhesion molecules with four known subtypes (1–4). Nectins aggregate in the brain at puncta adherentia junctions, sites that connect pre-and postsynaptic membranes (Takai et al., 2008). Nectin-1 is involved in CFC; protein levels of nectin-1 were increased in the synaptic fraction of ventral hippocampal matter following CFC (Fantin et al., 2013). The importance of nectin-1 specifically in the ventral hippocampus for the expression of CFC was confirmed by local infusion of R165, an anti-nectin-1 antibody serum that interferes with nectin-1 function. R165 infusion into the ventral hippocampus immediately after CFC reduced fear memory consolidation, as shown by reduced fear response when tested two- and seven days later, but these effects were not seen when R165 was infused into the dorsal tier (Fantin et al., 2013). CFC did not affect the expression of hippocampal nectin-3 in this study. However, since hippocampal nectin-3 is strongly involved in the effects of other types of stressors, including chronic restraint and early life stress, on learning and memory (van der Kooij et al., 2014; Wang et al., 2013, 2017), the possibility that the initial expression of hippocampal nectin-3 may be important as priming a condition for subsequent learning and memory related to CFC should not be overlooked.

Intra-synaptic processes are also expected to play an important role in the pathogenesis of PTSD. A recent report on a genome-wide DNA methylation study performed on the peripheral blood from combat veterans describes the investigation into underlying biological pathways based on the genes that were significantly associated with PTSD symptom severity (Mehta et al., 2017). The most notable pathway that emerged from this study involved regulation of the actin skeleton. Interestingly, another study showed that gene expression levels of an actin nucleator, Formin 2, were strongly reduced in peripheral blood from PTSD patients (Agis-Balboa et al., 2017). Cerebral actin dynamics, governed by actin binding proteins, are central mechanisms that determine the shape and function of synapses (Cingolani and Goda, 2008). It remains to be determined, though, to what extent the findings in peripheral blood of PTSD-patients (Agis-Balboa et al., 2017; Mehta et al., 2017) can be extrapolated to the brain. Impaired actin dynamics could explain the abnormal dendritic spine morphology found in the PTSD brain (Young et al., 2015) and be an important contributing factor underlying PTSD neuropathology. Several actin binding proteins have been identified that are directly regulated by stress and stress-related effectors, such as glucocorticoids and corticotropin-releasing hormone, incorporating the integral importance of stress in the neurobiology of PTSD (van der Kooij et al., 2016).

While an understanding of PTSD pathogenesis is important for the development of possible therapeutics, the ability to predict PTSD vulnerability factors could allow implementation of preventive measures. Identified vulnerability factors found in PTSD-patients include, among others, a dysregulation of the glucocorticoid-signaling pathway and single nucleotide polymorphisms at the glucocorticoid receptor and FKBP5 genes (van Zuiden et al., 2013). Therefore, these clinical findings, which suggest that abnormal regulation of the stress-regulating HPA axis may predispose individuals to an increased risk for developing PTSD, are congruent with the significance of pre-stressors and stress dysregulation in animal models for PTSD (Kim et al., 2013a, 2013b).

4.6. Treatment of fear memory disorders in humans; use of VR paradigms

4.6.1. Exposure therapy

Exposure therapy (ET) has proven effective in the treatment of anxiety disorders (Deacon and Abramowitz, 2004; McNally, 2007). During ET, the patient is repeatedly confronted with the feared object or situation until his/her distress level decreases (Bentz et al., 2010; Richard and Lauterbach, 2011). ET may be performed *in vivo* or *in sensu* (Craske et al., 2014). Moreover, Virtual Reality Exposure Therapy (VRET), *i.e.* confronting patients with their feared stimuli in Virtual Reality (VR), has successfully been implemented in treating anxiety disorders (Freeman et al., 2017; Opriş et al., 2012; Powers and Emmelkamp, 2008). VRET goes well with the emotional processing theory proposed by Foa and Kozak (1986), which suggests that, after being confronted with feared stimuli, the fear network is activated and can be modified by incorporating new, incompatible information into the network (Parsons and Rizzo, 2008). Furthermore, VRET puts special emphasis on perceptual cues, which have been shown to play a major

role in phobic fear (Shiban et al., 2016).

Being as effective as *in vivo* exposure (Anderson et al., 2003; Emmelkamp et al., 2002; Powers and Emmelkamp, 2008), VRET offers several advantages. A major advantage is the fact that the therapist can control the intensity, frequency and pace of the exposure, thus adapting the exposure to fit the patient's needs (Diemer et al., 2014). Being delivered in the therapist's office, VRET is not only performed in a safe environment but also offers considerable organizational and cost advantages (Emmelkamp, 2005; Opriş et al., 2012). Furthermore, physiological parameters like heart rate and skin conductance response (Diemer et al., 2014) as well as behavioral parameters (see Mühlberger et al., 2008) can easily be measured during VRET, thereby improving clinical assessment. With respect to the patients' attitudes toward treatment, acceptance is higher for VRET than for *in vivo* exposure (Garcia-Palacios et al., 2007).

4.6.2. How is VR used in treatment? Head mounted display and computer automatic virtual environment

During VRET, the virtual environment is presented to participants with the help of a head mounted display (HMD) or a computer automatic virtual environment (CAVE) (Krijn et al., 2004). A HMD (see Fig. 8) includes screens for both eyes, display optics, headphones and a tracking device for monitoring the participants' head position. Throughout exposure, the therapist can view the virtual environment presented to the patient *via* a user interface on a computer screen.

The CAVE (see Fig. 8 right) consists of a cubicle with the virtual environment being projected to its sides (Krijn et al., 2004). Both the patient and the therapist are inside this cubicle during exposure therapy (see Fig. 8 right).

4.6.3. Evidence

Being as effective as *in vivo* exposure, VRET has successfully been used in treating anxiety disorders (Opriş et al., 2012; Powers and Emmelkamp, 2008). VRET has proven effective in treating specific phobia like arachnophobia (Shiban et al., 2013), acrophobia (Emmelkamp et al., 2002; Krijn et al., 2004) or aviophobia (Cardoş et al., 2017; Mühlberger et al., 2003). As for *in vivo* exposure (see Öst et al., 1997), there is evidence to show that a single session of VRET can produce significant treatment effects (Mühlberger et al., 2003). Furthermore, VRET has successfully been used in the treatment of panic disorder (Botella et al., 2011), social phobia (Anderson et al., 2003; Klinger et al., 2005) and PTSD (Difede et al., 2007; Rothbaum et al., 2001). Overall, a significant expansion of VR in psychotherapeutic practice and clinical contexts is expected (Diemer et al., 2015).

4.6.4. Special issues related to VR therapy: immersion and presence

Immersion and presence are two closely related but distinct concepts (Price et al., 2011). Immersion refers to technical aspects (field of view, display resolution) of the system used, *i.e.* its capability to represent the real world with respect to different modalities (Krijn et al., 2004; Slater, 2003). Immersion influences presence, which refers to the extent to which individuals perceive the virtual environment as real and feel connected to it (Krijn et al., 2004; Price et al., 2011; Schubert et al., 2001). Research suggests that presence is important but not sufficient for successful VRET (Diemer et al., 2015; Price and Anderson, 2007).

4.6.5. Limitations

VRET fails to induce anxiety in some patients which may impede treatment efficacy (Anderson et al., 2005; Diemer et al., 2014). VR sometimes causes nausea, dizziness, or headache (Bush, 2008). In order to prevent simulator sickness, the VR has to be designed appropriately and patients susceptible to motion sickness should not undergo VRET (Hoffman et al., 2001). Furthermore, keeping exposure short (< 20 min) or providing breaks during the sessions could reduce the risk of simulator sickness (Gujjar et al., 2017; Hoffman et al., 2001).

Lastly, even though VRET has proven effective, it is rarely used in practice to date. Therapists may be reluctant to use VR due to high costs for purchasing the devices needed, or because they are not familiar with the intervention methods (Rothbaum et al., 2000).

4.6.6. Outlook

There are several technological innovations VRET might benefit from. With the help of physiological measures or movement tracking, the virtual environment could automatically be adapted in a way that fosters treatment outcome (Lindner et al., 2017). Furthermore, using augmented reality (*i.e.* virtual objects, such as feared stimuli, being integrated into the patient's perception of the real environment) may increase the feeling of presence during exposure as well as the ecological validity of VRET (Baus and Bouchard, 2014; Botella et al., 2011; Dünser et al., 2011). Finally, it is important to provide affordable and user-friendly devices in addition to training programs for therapists in order to foster clinicians' acceptance of VRET (Botella et al., 2017).

5. Use of autobiographical memory for coding, diagnosis, and treatment of fear memory disorders

5.1. Coding of earliest fear-related memories, as part of autobiographical memory

From an evolutionary perspective, the precise coding of a threatening event is important in order to be prepared for future threats. From a very early age, humans are programmed to use emotional information to understand potentially threatening situations. A number of studies have shown that as early as 6–12 months of age, infants start to display an attentional bias toward fearful facial expressions (Leppänen and Nelson, 2009; Peltola et al., 2012). During the life course, events that are credited as more important during encoding are better remembered over time (Wittmann et al., 2005). In general, emotional information is often better remembered than neutral information. Arousal response, often related to the emotional events, elicit emotion-

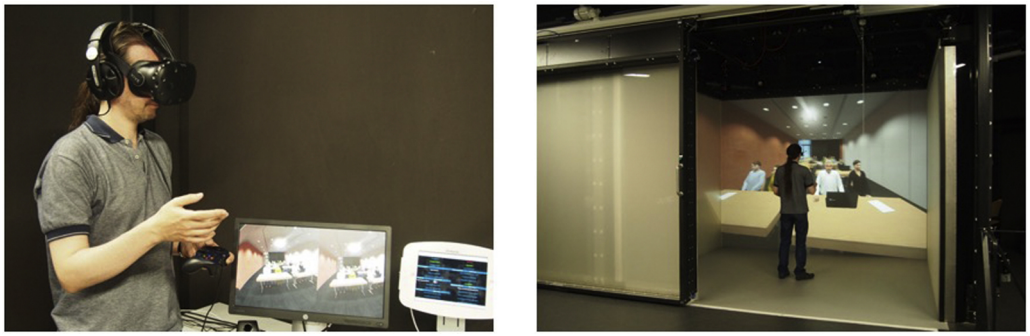

Fig. 8. *Left panel.* Head mounted display (HMD) and virtual environment presented. *Right panel.* Example of the CAVE paradigm. Figure adapted from Fig. 1 in Pinna (2018).

specific processes, which enhance both encoding, consolidation and retrieval of event-related memory (Kensinger, 2009). Emotionally arousing experience results in the engagement of adrenergic and cortisol stress-hormone systems in the amygdala that interact to promote memory storage in the cortex (McGaugh, 2004). On the other hand, under conditions of severe stress, people may focus almost exclusively on survival and endurance, and the attentional focus is narrowed. This can result in poor memory for the events that elicited emotion (Deffenbacher et al., 2004).

The most important episodes in life constitute the autobiographical memory, "the explicit memory for specific points in the past, recalled from the unique perspective of the self in relation to others" (Nelson and Fivush, 2004).

It starts to develop at the age of 5–6 years and earliest memories are regarded as integral parts (Nelson and Fivush, 2004; Peterson et al., 2005). Episodic autobiographical elements, such as reference to oneself as a part of the memory and emotionally significant events, develop later than semantic autobiographical memory, which is knowledge that the events happened (Piolino et al., 2007). It is noteworthy that reviewing the contents of certain events (*i.e.* episodic memory) enhances the memory of those events (Finley et al., 2011; Koutstaal et al., 1998). Therefore, early memories that are frequently discussed and reviewed with a parent, for example, are strengthened.

The research is quite unanimous about the fact that people cannot remember events from their first three years of life, and that memories will become inaccessible later on, which eventually results in childhood amnesia (Peterson et al., 2009; Tustin and Hayne, 2010). A core precondition for verbal recollection of an experience is sufficient linguistic capacity at the time of encoding a memory (Morrison and Conway, 2010; Nelson and Fivush, 2004). Simcock and Hayne (2002) observed that children could not verbally report information about an event that they had experienced at the age of 2–3 years if it involved issues that were not yet part of their productive vocabulary.

However, intensive fear and prolonged stress might have an impact on the formulation of very early memories. The study with a non-human sample by Callaghan and Richardson (2012) showed that rat pups experiencing a stress response from early maternal separation had enhanced early memories for fear: rat pups subjected to maternal separation early in their development responded with longer retention of fear memories formed during infancy in comparison to the non-stressed control group. Callaghan and Richardson concluded that adverse environments in infancy lead to longer retention of childhood memories. They also concluded that this reflects an early transition into the adult-like memory system, an effect that is mediated by exposure to the stress hormone corticosterone, the rodent form of cortisol. This offsetting effect of a stress response related to parental separation on childhood amnesia has not yet been demonstrated in human children. However, it has been observed that people with prolonged childhood maltreatment elicit elevated levels of fear and anxiety as a response to the script-driven imagery of personalized trauma narratives (Lanius et al., 2001, 2003) as well as to the standardized scripts focusing on arousal of safety concerns (McTeague et al., 2010). Especially, anxious people are likely to have anxiety-related memory bias of events that have ambiguous meaning, eliciting emotional interpretation (MacLeod and Mathews, 2004).

Fear as an emotion can both enhance the encoding of certain parts of an event *and* narrow the encoding of other parts, as mentioned briefly above. First, "tunnel memory," or the emotional memory narrowing (Kensinger, 2009), happens when increasing emotional arousal results in attention narrowing to features that are of central importance to events; later on, these details are more strongly remembered. At the same time, peripheral details are not encoded (Christianson and Loftus, 1991). The phenomenon of earliest memories becomes even more complex when looking at the evidence showing that memories may include errors concerning when an event happened, what happened, where it happened, and who was involved. It is also possible that a person "remembers" totally false events – even childhood sexual abuse – if he/she is exposed to misleading information (Loftus and Bernstein, 2005; McNally et al., 2004).

Remembering is always a process of mental reconstruction, meaning that current challenges and stressful events can influence what we remember (Conway, 2005). According to the Self-Memory System model of autobiographical memory, memories that are coherent with and confirm one's goals and self-images are more accessible. This could be why earliest fear-related memories do not have same importance to all individuals. Interestingly, "only" a third of war-affected Palestinian children reported traumatic events and accidents as their earliest memory, while 43% reported pleasant memories of play and nice places (Peltonen et al., 2017). Their occurrence closely corresponds with earliest memories in studies among children living in peaceful and safe environments (Mullen, 1994). This might be interpreted as evidence for individual trajectories concerning the significance of earliest fear-related events as a part of autobiographical memory.

Empirical evidence of gender differences on children's autobiographical memories is mixed. Some studies show that girls report more traumatic situations and more significant transitions (Peterson et al., 2005) with more narrative, coherent, and longer descriptions (Tizzard-Drover and Peterson, 2004). Others show no significant gender differences in the content or structure of children's autobiographical memories (*e.g.*, Burgwyn-Bailes et al., 2001; Fivush et al., 2008).

Taken together, it can reasonably be assumed that the earliest fear-related events would be central parts of human autobiographical memory. Due to childhood amnesia and mental reconstruction of memories, it is, however, extremely difficult to study the prevalence or centrality of such events. More research of fear and autobiographical memory is needed, especially among children, as we know that access to early childhood memories becomes more difficult with age.

5.2. Autobiographical memory in affective disorders, including fear-related disorders

The concept of episodic memory was originally coined by Tulving (1972), and although there is still no general consensus pertaining to the core components of episodic memory (Zlomuzica et al., 2014), autobiographical memory (AM) is considered as a specific type of episodic memory that involves the recollection of an individuals' personal experiences of specific events. In accord with Conway and Pleydell-Pearce's (2000) model, AMs are organized *via* a hierarchical three-tiered structure, ranging from (1) broad lifetime periods, (2) more general events, and (3) event specific knowledge; the latter includes specific episodic memories. This enables an individual to retrieve personally relevant information using different levels of abstraction. A large body of literature has demonstrated that individuals with depressive-, stress- and fear-related disorders are vulnerable to exhibiting impaired episodic autobiographical memories (*e.g.*, Airaksinen et al., 2005; Griffiths and Lovick, 2005; Williams et al., 2007). Importantly, affective disorders, including fear-related disorders, lead to disruptions in the hierarchical search process resulting in over-general memories (Griffith et al., 2012; Hitchcock et al., 2017). Over-general autobiographical memory (OGM) is associated with a number of emotional disorders, particularly depression, trauma and stress-related disorders (*e.g.*, Kangas et al., 2005; Moore and Zoellner, 2007; Moradi et al., 2014; Williams et al., 2007). However, evidence for OGM is more variable for other types of fear disorders (Hitchcock et al., 2017; Wenzel et al., 2004). OGM is characterized by difficulties in the retrieval of specific personal memories. Notably, individuals with OGM deficits retrieve more generic or broad-based memories that cover an extended period of time. They are also susceptible to retrieving more categorical memories (*e.g.*, 'taking baths is a relaxing time for me'). Importantly, OGM is a unique facet of cognition as this memory deficit is not fully explained by generalized memory deficits or lower IQ (Griffith et al., 2012).

Conceptual models (Beck and Clark, 1997; Ehlers and Clark, 2000; Foa and Kozak, 1986) and empirical studies suggest that the susceptibility of individuals with affective disorders to bias toward over-general processing of autobiographical information is a protective mechanism, as this facilitates avoidance associated with negative emotional experiences (Wenzel et al., 2004). Fear-related disorders also lead to biases toward negative valence memories with reduced access to positive valence memories.

5.2.1. Assessment and coding of autobiographical memory functioning

A number of methods have been utilized to assess AM functioning, including the detection of OGM deficits (for review, see Griffith et al., 2012). To date, the most commonly used AM assessment paradigm is the Autobiographical Memory Test (AMT). The AMT was developed by Williams and Broadbent (1986): in their seminal work, they found that suicidal patients retrieved significantly more over-general memories compared to both clinical and healthy controls. The AMT is a cuing paradigm and currently considered the 'gold standard' measure of AM, with adequate psychometric properties (Griffith et al., 2012).

The AMT involves presenting a combination of positive valence (*e.g.*, 'happy') and negative valence (*e.g.*, 'sad') stimulus cue words, and the individual is asked to elicit the first specific personal memory that comes to mind. Some studies have also used neutral cue words (*e.g.*, 'beach'). A specific memory is defined as a particular event that occurred at a specific time and place. For example, a specific memory to the cue 'excited' could be 'I was very excited last Sunday when one of my closest friends from overseas visited me.' Typically, no time period restrictions are provided; that is, the specific memory can occur from any time period in a person's life, referred to as 'unconstrained AM.' However, some experimental studies have used the AMT by imposing a 'constrained memory' period; in particular, asking participants to generate specific memories in response to a restricted period in their life (*e.g.*, 'since the time you were diagnosed with cancer'; Kangas et al., 2005). Participants are also required to retrieve a new specific memory in response to each cue word presented – repeat memories are not coded as specific memories.

Five type of coding categories are typically used with the AMT, including the proportion of (1) specific memories retrieved; (2) extended memories which go beyond a single day; (3) categorical memories; (4) semantic associations, and (5) omissions (*i.e.*, no general or specific memory is generated within the set time period). Latency of response is also coded; specifically, the time taken to generate the first specific memory to the stimulus cue within the allotted time period is recorded. Typically, individuals have 30 to 60 s to generate a specific memory, with some variability between studies (Griffith et al., 2012). Feedback is usually not provided to individuals during testing. However, some studies have used prompting if a specific memory is not initially reported within the allotted time.

Over the last decade, a number of variations to the AMT have been tested. These include a minimal instructions version (Debeer et al., 2009), the Sentence Completion for Events of the Past Test (SCEPT; Raes et al., 2007) and the TEMPau (the Test Episodique de Memoire du Passe autobiographique; Piolino et al., 2009) (for review, see Griffith et al., 2012). Given the variability of formats available for the AMT, this may partially explain the mixed findings in the literature pertaining to which individuals are more vulnerable to experiencing AM deficits (*e.g.*, D'Argembeau et al., 2006; Morgan, 2010; Wenzel et al., 2004). In particular, variability exists between AMT protocols administered in terms of types of coding categories used; stimulus cue format (verbal/oral *vs.* visual or both); type of cue words and types of valence tested (*i.e.*, negative, positive *vs.* neutral cues) as well as number of cues used; and format of testing (computer generated cues *vs.* face to face).

Wenzel et al. (2004) proposed that there is variability in the types of anxiety-related memories activated between specific types of anxiety disorders, which may further explain the mixed findings that have emerged in studies investigating memory biases toward threat in individuals with fear disorders. Notably, PTSD and panic disorder (PD) consist of memories that have more salient and vivid properties compared to memories based on more social and generic worries as defined by Generalized Anxiety Disorder (GAD) and social anxiety disorder (SAD). In fact, Wenzel et al. (2004) found some support for this proposition, as trauma-related memories were reported to be most vivid and more likely to generate intense negative emotions relative to generalized worry and social-related memories. They further posit that PTSD and PD are associated with events that are more fear provoking and unexpected, which may contribute to activating memories that are more vivid and sensory in detail relative to more generic and social-oriented experiences. Indeed, there is evidence to further support this latter proposition. Studies have shown that individuals with PTSD experience vivid and sensory recollections of their traumatic experience, which facilitates the maintenance of this disorder by way of avoiding cues that activate trauma-induced memories. Moreover, impaired retrieval of specific trauma-related memories within the initial month post-trauma have been found to be predictive of PTSD severity overtime (*e.g.*, Harvey et al., 1998; Kangas et al., 2005). Conversely, there is evidence that indicates individuals with SAD recollect past social experiences with more self-referential information but less vivid sensory information (including visual and auditory details), contributing to distorted self-perceptions and disrupting processing of past social experiences, thus facilitating the maintenance of SAD symptoms (D'Argembeau et al., 2006; Morgan, 2010). Taken together, this body of literature indicates that affective disorders are associated with AM deficits, although there is variability in the specific type of deficits elicited contingent on whether the memory is associated with a trauma or intense fear-related event rather than more general, diffuse and socially-oriented experiences. This has implications in terms of treatment interventions that have been developed to specifically target AM training.

5.2.2. Treatment of AM in fear disorders

Over the past decade, several novel cognitive-based interventions have been developed which focus on targeting OGM deficits, referred to as 'autobiographic episodic training' (AET). Hitchcock et al. (2017) define AET as 'any training protocol that targets either retrieval of past autobiographical episodes or projection of future autobiographical episodes, with the aim of modifying processing biases (*e.g.*, overgeneralization, reduced salience of positive material)' (p. 94). There are several different types of AET programs which have been developed to date, including Memory Specificity Training (MEST; Raes et al., 2007), Concreteness Training (Watkins et al., 2009), Competitive Memory Training (COMET; Ekkers et al., 2011); and variations of the Cognitive Bias Modification (CBM) paradigm. The MEST, COMET and concreteness training have all been initially tested with depressed samples. This is not surprising, given that OGM is a robust finding in the depressive literature over the past three decades. More recently, the efficacy of MEST, COMET and variants of the CBM have been tested with trauma and anxiety samples.

The MEST, which was developed by Raes et al. (2007), is a 4-session group training intervention in which individuals are required to practice recalling specific memories in response to negative, positive or neutral cue words over a 4-week interval. Psychoeducation is an initial component of this program, whereby participants are introduced to the different types of AM categories (*i.e.*, extended, categorical and specific). The MEST also includes structured homework based on repeated practice of generating specific memories to cue words to enable generalization of skills to daily experiences.

Watkins and Moberly (2009) designed the 6-week concreteness training paradigm with the objective to improve individuals to recall specific negative daily experiences in a more concrete way by completing a series of daily training exercises. Imagery is used as part of this process specifically to focus on the sensory detail of recollected experiences.

The COMET program was developed by Ekkers et al. (2011) and has also been tested in group format, typically in 7–8 sessions. The aim is to learn to preferentially recall positive memories. This is based on Brewin's theory of competitive memory retrieval hierarchies (Brewin, 2006), focusing on changing access to more positive material relative to negative memories facilitated by use of imagery and positive self-verbalizations. A number of COMET protocols have been developed for specific psychopathologies, including changing memory representations associated with worry, rumination and self-esteem (for review, see Hitchcock et al., 2017).

Variations of the CBM paradigm have been tested to improve AM functioning by utilizing imagery-based CBM. This involves practicing imagining more positive outcomes for ambiguous scenarios presented. In particular, the aim is to train individuals toward a more positive bias in recollecting positive outcomes for ambiguous events whilst also training individuals to generate more positive specific outlooks for the future (*e.g.*, Lang et al., 2012).

Hitchcock et al. (2017) recently published a meta-analytic review based on evaluating 15 randomized controlled trials (RCTs) that compared an AET program to a control condition in adult samples with a clinician-derived major depressive disorder (MDD) or anxiety and stress-related disorder. The majority of the trials identified ($n = 12$) tested the efficacy of the AET paradigm with individuals with MDD, whilst two studies were based on samples with anxiety disorders, and one study used a sample of individuals diagnosed with PTSD. A small effect was found for the efficacy of AET on depressive symptoms for MDD samples ($d = .32$), with the strongest evidence for COMET (although this is in part due to more studies to date having tested COMET relative to other types of AET paradigms). The two anxiety-based AET studies also utilized the COMET paradigm – one with an Obsessive Compulsive Disorder (OCD) sample (Schneider et al., 2015), and the other with individuals with PD (Korrelboom et al., 2014). In the OCD study, no differences in change of OCD symptoms were found for the COMET relative to control condition. In the PD study, the COMET was compared to a group-based Applied Relaxation program, and both programs were found to be significant in reducing panic symptoms with no differences evident between groups. The only RCT identified for stress-related conditions was based on a small sample of 24 Iranian combat veterans with PTSD who either received MEST for 5-sessions or were randomized to a no-intervention control condition (Moradi et al., 2014). Findings revealed support for the MEST program, with participants reporting significant reductions in PTSD symptoms as well as improvements in specific memory recall, persisting at a 3-month follow-up mark.

Collectively, for fear disorders, the AET paradigm is very much in its infancy. Although the outcomes from the Moradi et al. (Moradi et al., 2014) and Korrelboom et al. (Korrelboom et al., 2014) studies are promising, more research using larger samples is clearly warranted. Taking into account the MDD studies, Hitchcock et al. (2017) conclude that the current evidence for AET for MDD is of moderate strength, but more research is needed to establish whether AET is efficacious as a standalone treatment, or whether it is more efficacious when included as a module of more established treatments for depression. This recommendation would also eventually extend to fear-related disorders. Moreover, in accord with Hitchcock et al.'s (2017) recommendations, the possibility of integrating components of AET programs to simultaneously target both improving memory bias and specificity whilst also enhancing positive memory retrieval and generation of future projected expectancies is a fruitful avenue for future intervention studies in this field. This line of inquiry has direct relevancy for fear disorders given these are maintained by fear of recurrence and/or biased expectations of future experiences.

6. Linguistics

With this understanding of the current state of anxiety and fear research as a backdrop, our team was specifically tasked to review the language that people use to express feelings related to anxiety and fear. Within the realm of affective research, confusion arises over the fact that some feelings are a component/constituent of emotional responses. For example, fear as an emotion consists of a continuum of automatically activated defense behaviors (Kozlowska et al., 2015) that co-occur along with "feelings of fear". Consequently, the term *feeling* is often used incorrectly as a synonym for *emotion* and *vice versa* (LeDoux, 2015a; Munezero et al., 2014). But feelings are not emotions *per se* (LeDoux, 2015b) which tend to be more complex (Fontaine et al., 2007), and feelings are not limited to those that co-occur with specific emotions. Rather, feelings encompass a wide range of important mental experiences such as signifying physiological need (*e.g.*, hunger), tissue injury (*e.g.*, pain), optimal function (*e.g.*, well-being), the dynamics of social interactions (*e.g.*, gratitude), *etc.* (Damasio and Carvalho, 2013) Additional challenges relate to the fact that feelings are not consistently defined, and that our definitions for these terms can evolve over time (Tissari, 2016). Moreover, while some feelings may be universally experienced across cultures (*e.g.*, hunger, pain, cold, fatigue, *etc.*), other feelings are understood to be culturally constructed (*e.g.*, gratitude (Boiger and Mesquita, 2012), optimism (Joshi and Carter, 2013)). As a result, the Human Affectome Project taskforce agreed that any attempt to create a linguistic inventory of articulated feelings would need to first define feelings in a manner that can help us understand the full range of terms to be considered and then undertaken with an acute awareness that variations in terminology are going to exist in day-to-day usage, between languages, and across cultures. So, a definition for feelings was developed as part of the project. A small task team within the larger effort reviewed the literature to create a definition for feelings that could serve as a starting point. The task team produced a first draft and shared it with the entire taskforce of nearly 200 researchers, feedback/input was gathered, and then it was refined, redistributed and the process iterated several times to achieve broad consensus within the group. The resulting definition is as follows:

> A "feeling" is a fundamental construct in the behavioral and neurobiological sciences encompassing a wide range of mental processes and individual experiences, many of which relate to homeostatic aspects of survival and life regulation (Buck, 1985; Damasio and Carvalho, 2013; LeDoux, 2012; Panksepp, 2010; Strigo and Craig, 2016). A broad definition for feeling is a perception/appraisal or mental representation that emerges from physiological/bodily states (Damasio and Carvalho, 2013; LeDoux, 2012; Nummenmaa et al., 2014), processes inside (e.g., psychological processes) and outside the central nervous system, and/or environmental circumstances. However, the full range of feelings is diverse as they can emerge from emotions (Buck, 1985; Damasio and Carvalho, 2013; Panksepp, 2010), levels of arousal, actions (Bernroider and Panksepp, 2011; Gardiner, 2015), hedonics (pleasure and pain) (Buck, 1985; Damasio and Carvalho, 2013; LeDoux, 2012; Panksepp, 2010), drives (Alcaro and Panksepp, 2011), and cognitions (including perceptions/appraisals of self (Ellemers, 2012; Frewen et al., 2013; Northoff et al., 2009), motives (Higgins and Pittman, 2008), social interactions (Damasio and Carvalho, 2013; Gilam and Hendler, 2016; LeDoux, 2012; Panksepp, 2010), and both reflective (Holland and Kensinger, 2010) and anticipatory perspectives (Buck, 1985; Miloyan and Suddendorf, 2015)).
>
> The duration of feelings can vary considerably. They are often represented in language (Circanski et al., 2012) (although they can sometimes be difficult to recognize and verbalize) and some feelings can be influenced/shaped by culture (Immordino-Yang et al., 2014). Feelings that are adaptive in nature (Izard, 2007; Strigo and Craig, 2016) serve as a response to help an individual interpret, detect changes in, and make sense of their circumstances at any given point in time. This includes homeostatic feelings that influence other physiological/body states, other mental states, emotions, motives, actions and behaviors in support of adaptation and well-being (Damasio and Carvalho, 2013; Strigo and Craig, 2016). However,

some feelings can be maladaptive in nature and may actually compete and/or interfere with goal-directed behavior.

A "feeling" is not a synonym for the term "emotion". There is standing debate between researchers who posit that discrete emotion categories correspond to distinct brain regions (Izard, 2010) and those who argue that discrete emotion categories are constructed of generalized brain networks that are not specific to those categories (Lindquist et al., 2012). However, both groups acknowledge that in many instances feelings are a discernable component/constituent of an emotional response (which tends to more complex).

Using this definition of feelings as a starting point, the linguistics task team then undertook a formal linguistic analysis and ultimately proposed nine broad categories of feelings (*i.e.*, Physiological or Bodily states, Attraction and Repulsion, Attention, Social, Actions and Prospects, Hedonics, Anger, General Wellbeing, and Other).

Feelings related to anxiety and fear were found in the Actions and Prospects category which was described as "*Feelings related to goals, tasks and actions (e.g. purpose, inspired), including feelings related to planning of actions or goals (e.g., ambitious), feelings related to readiness and capacity of planned actions (e.g. ready, daunted), feelings related to levels of arousal, typically involving changes to heart rate, blood pressure, alertness, etc., physical and mental states of calmness and excitement (e.g. relaxed, excited, etc.), feelings related to a person's approach, progress or unfolding circumstances as it relates to tasks/goals within the context of the surrounding environment (e.g. organized, overwhelmed, surprised, cautious, etc.), feelings related to prospects (e.g. afraid, anxious, hopeful, tense, etc.)*" We reviewed the feelings found in this category of this linguistics analysis and conducted a review of this language that people use to convey feelings related to anxiety and fear.

6.1. Value of the development of linguistic tools for assessments and treatment of fear learning and memory disorders

As described in the last three sections, subjective experiences and autobiographies are valuable for analyzing fear and fear-related memories across people. In addition, these analyses would be valuable for longitudinal analyses in individual clients or patients and to measure response to behavioral and/or pharmacological interventions. They could be used to assess fear and fear-related memories in individuals as part of challenging missions, such as deep space missions of astronauts. Thus, we suggest that linguistic analysis should be further developed and incorporated into standard care.

One approach to analyze autobiographical writings could be using an unbiased approach exploring relationships between words – either words that occur together within 2–4 words or words that are being used in the same text. For example, "tidytext" offers methods for calculating and visualizing relationships in a given sample (https://www.tidytextmining.com/ngrams.html). Interestingly enough, this approach resembles the kind of analysis being used in systems biology to assess relationships in large sets of biological data, seen in work from researchers like Ovidu Iancu at the Portland V.A. Medical Center and OHSU.

In contrast to the unbiased approach, text analysis could be biased and based on the presence of specific words related to fear. The words initially categorized as pertinent to anxiety and fear in this project were categorized by the co-authors in one of the following categories: (1) safety - internal; (2) safety - external; (3) anxiety - internal; (4) anxiety - external; (5) fear - internal; (6) fear - external; or (7) other. In addition, each word was rated using the following scale of intensity: 1: very mild; 2: mild; 3: medium; 4: strong; and 5: very strong. Realizing that being a native English speaker or not might affect the categorization and intensity ratings of these words (see also the section below regarding the importance to consider cross-cultural issues regarding language and feelings), we compared the responsive of the native and non-native English speaking co-authors.

For the intensity ratings, we first ran a repeated measures ANOVA comparing the rankings identified by native and non-native English speakers; from this, we found significant main effects of word ($p < 0.0001$, $F(41,574) = 16.14$), speaking status ($p < 0.05$, $F(1,14) = 5.459$), and a significant interaction of speaking status and word ($p < 0.01$, $F(41,574) = 1.780$). We then divided the analysis in words rated between 1–3 and 3–5 separately and used a repeated measures ANOVA. For the less severe-rated words (rated between 1–3), analysis revealed a main effect of word ($F(20,278) = 2.106$, $p < 0.01$) and an overall significant difference between native and non-native speakers ($F(1,278) = 48.93$, $p < 0.0001$). There was a distinct group of words that were rated with higher intensities by non-native speakers, such as "disquietude" and "eerie" (Fig. 9A). For the other words rated

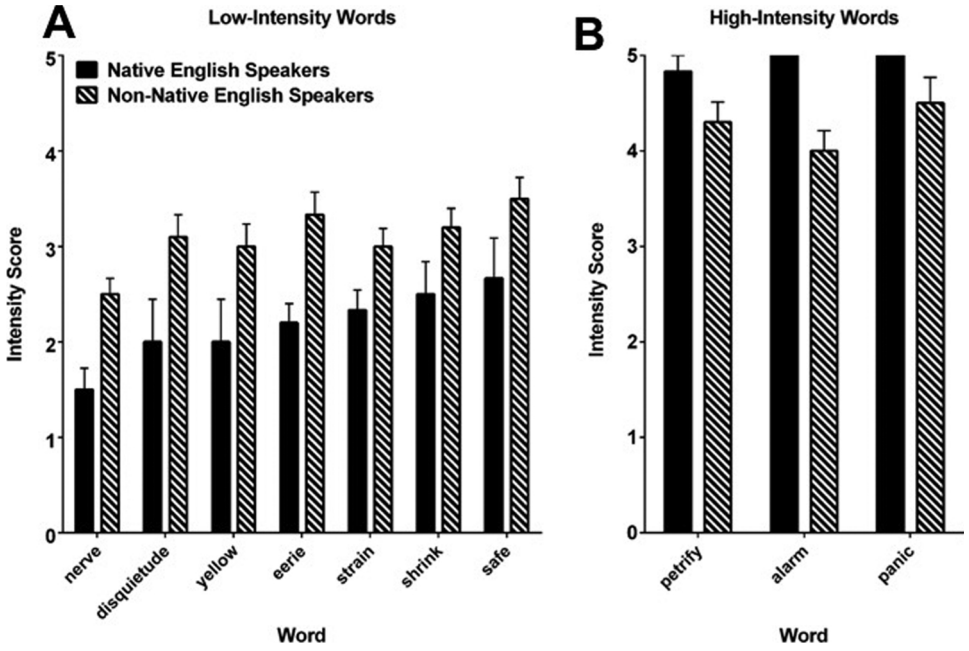

Fig. 9. Intensity rating of low-intensity (A) and high-intensity (B) words of native and non-native English speakers.

Table 3
(A) Non-significant words identified as "low intensity" (rank 1–3) by most raters. (B) Non-significant words identified as "high intensity" (rank 3–5) by most raters.

A			B		
Word	Native	Non-native	Word	Native	Non-native
nervous	2.17	2.50	serious	3.00	3.70
uneasy	2.17	2.70	superimminent	3.20	3.50
shaky	2.33	3.00	anxiety	3.33	3.60
timid	2.50	2.50	menace	3.50	3.10
security	2.50	3.22	intimidate	3.50	3.20
secure	2.50	3.70	fear	3.50	3.60
recreant	2.60	3.38	scare	3.50	3.90
humanize	2.60	3.83	fright	3.50	4.00
vulnerable	2.67	2.80	trepidation	3.83	3.20
queasy	2.67	3.00	frighten	3.83	4.40
awe	2.67	3.40	dread	4.00	4.30
safe	2.67	3.50	graver	4.17	4.30
worry	2.83	3.00	grievous	4.17	4.30
afraid	3.00	3.10	shock	4.17	4.30
apprehend	3.00	3.20	terror	4.67	4.89
craven	3.00	3.63	terrify	5.00	4.90
			horror	5.00	5.00

between 1–3, there were no differences in mean ratings between the groups (Table 3A). For the more severe-rated words (rated between 3–5), the opposite pattern was seen, with native speakers rating specific words higher, such as "alarm" (Fig. 9B). For the other words rated between 3–5, there were no differences in mean ratings between the groups (Table 3B). Importantly, none of the words that were part of the set for which a group difference was seen in either the 1–3 or 3–5 severe range were unfamiliar to non-native speakers. In contrast, some of the words for which there were no group differences, like "queasy," were less or not familiar among non-native speakers.

For comparing the categorization of the words in native and non-native speakers, we collaborated with co-author Dr. Jessica Minnier, a biostatistician at OHSU with special expertise in the analyses of large data sets. The relative distance between (1) safety internal; (2) safety external; (3) anxiety internal; (4) anxiety external; (5) fear internal; and (6) fear external was discussed and agreed upon by co-authors Boutros and Raber (Table 4). Subsequently, this information was used to compare the distance of the categorized words for each co-author who contributed feedback for this analysis. Potential group differences were assessed comparing the distances between words of native and non-native speakers using generalized estimating equation (GEE) regression, which is often used to analyze correlated response data. As a control, we compared the distances between words of two computer-generated randomized groups that each included native and non-native speakers.

When creating the distance matrix, the average score between each pair of root words across all raters, non-native, and native English speakers is used to explore dissimilarity and similarity in categorization. Larger distances mean that the scoring categories are more dissimilar.

Words were clustered with a complete-linkage hierarchical clustering, which can be visually seen in Fig. 10. A Mantel Test was performed to compare the distance matrices of non-native and native English speakers and to measure the correlation of all entries, with random permutations calculated to determine the p-value. There was a correlation of $r = 0.67$ with $p < 0.001$, suggesting a positive correlation between native and non-native distances. In this preliminary proof-of-concept analysis, it is clear that primary language is an imperative factor that should be considered, and has the potential to be informative in linguistics analysis.

Next, the difference between distance matrices of non-native and native speakers was calculated, and a permutation test on the norm (sum of all the matrix cells squared) of the matrix of differences was performed. The obtained p value, the proportion of randomly permuted norms that are larger than the observed norm, was 0.061. This result is not significant at type I error 5%, but even with the small sample sizes within each group, the observed norm is quite large compared to the distribution of randomly permuted norms and this suggests that the two distance matrices are quite different. Hence, this further suggests that primary language may be associated with perceived dissimilarities between words. An increased sample size is needed to confirm this association.

A strength of the two distinct analyses described above (*i.e.*, intensity rating and categorization of words) is that universal principles could be further developed, tested, and validated that would allow quantification of fear and fear-related memories in various populations of both native and non-native English speakers of diverse cultural backgrounds around the world. Based on the available data, there is good reason to believe that the same approach would work well in children, adults, and the elderly. This would be particularly helpful for global mental health efforts, as it may be possible to utilize the hierarchy of fear-related words to further development of fear ratings, regularly used in CBT-based interventions as a measure of conscious fear (see the argument for importance of subjective reports of fear and anxiety, LeDoux and Hofmann, 2018).

Similarly to the predictive nature of future cognitive impairments discovered in texts analyzed from nuns (Barnes et al., 2003), one can see how written texts could be used to assess mental health and follow annual changes in mental health. This has the potential to be especially insightful for those with challenging assignments, including soldiers during and following deployment, emergency teams responding to natural and terrorism-related disasters, astronauts during and following space missions, and those that are part of populations at increased risk to develop fear-related disorders. Moreover, this could be valuable for flagging individuals who might be at increased risk to harm themselves and/or others. Based on research following shootings or other attacks at schools and crowded, public events, it is often noted that suspects often drafted and posted concerning texts in e-mails, web sites, or social media accounts.

We realize that the basis of the above analyses is the presence of fear-related words, which is a potential limitation. The absence of fear-related words will be important to include in the analysis as well, especially in those who suppress their use because of severe traumatic memories and attempts to avoid reliving them. The suppression could be expressed continuously or transiently, as part of a cycle, thus highlighting the importance of considering longitudinal analyses to detect either increases or decreases in the use of fear-related words, which could be used as part of assessments and treatments. Linguistic analysis is, therefore, an important factor to consider, just as environment, experiences, and genetic and epigenetic factors related to the susceptibility or resilience to fear-related memories are considered in patients.

Table 4
Definition of "distance" between word categories used for statistical analyses, defined by authors Boutros and Raber.

	Safety-Internal	Safety-External	Anxiety-Internal	Anxiety-External	Fear-Internal	Fear-External
Safety-Internal	0	1	2	2.5	3	3.5
Safety-External	1	0	2.5	2	3.5	3
Anxiety-Internal	2	2.5	0	1	2	2.5
Anxiety-External	2.5	2	1	0	2	2.5
Fear-Internal	3	3.5	2	2.5	0	1
Fear-External	3.5	3	2.5	2	1	0

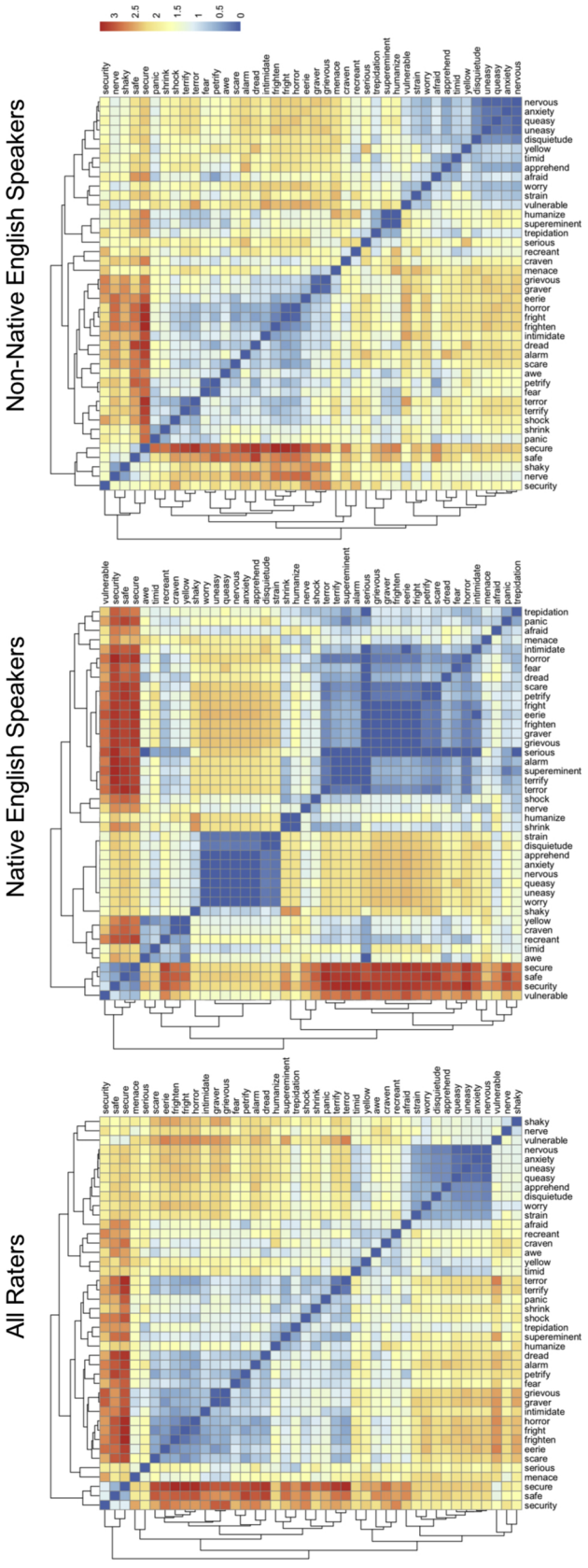

Fig. 10. Heat maps representing the complete-linkage hierarchical clustering. (A) A Mantel Test was performed comparing the distance matrices (middle and right panels), revealing a correlation coefficient of 0.67 and a p value < 0.001. *Left panel.* Heat map of all raters together. *Middle panel.* Heat map of Native English speakers only. *Right panel.* Heat map of non-native English speakers only.

6.2. How well can the main categories of the linguistics framework and the feelings related to fear inform the neuroscience of fear learning and memory in health and disease?

Although an important question to address, it seems premature to answer it at this point in time. It is still unclear whether the absence – rather than the presence – of specific words might be more informative to detect fear learning and memory alterations in health and disease and how specific use might be altered over time following a traumatic event. Additionally, it is unclear whether a linguistic approach like this would work better or worse in children, adolescents, or adults. Finally, a remaining unknown factor is the feasibility of comparing results from this approach across distinct languages and cultural settings.

6.3. Are there important cross-cultural issues regarding language and feelings to consider?

As described above, in the relatively small sample of co-authors on this paper, we detected a profound difference in the intensity ratings of the analyzed words in native and non-native English speakers. This highlights the importance to consider cross-cultural distinctions regarding language use. In addition to primary language differences, it is conceivable that there might be considerable cultural differences in language use in second- and third-languages that would need to be explored. It is similarly conceivable that there might be profound differences depending whether or not there are severe environmental challenges (extreme poverty, famine, war or terrorism-prone zones, environments with increased criminal gang-related activities, *etc.*). The developmental perspective might also take into account the differences in acquisition of fear-related vocabulary among children living in threatening *versus* non-threatening environments. In order to grasp the issues of cultural and environmental settings, we checked whether there were differences in frequency and variety of fear related words when 9–12 year-old children described their earliest memories in Gaza (n = 110) and in Finland (n = 148). We found out that none of the children in Gaza and only one in Finland used a fear-related word in their descriptions, although 29% of children in Gaza and 7% in Finland described an event that was related to a trauma or accident. This observation shows that the threat of the environment would not be linked to a differently emerging fear vocabulary among children. On the contrary, the developmental stage as such could play a role. Among Finnish adults (19–61 years old), 16% used one or more fear related word in their description of earliest memory. Interestingly, only 9% described an event that was related to trauma or accident. This means that many adults – unlike the children – described an event to contain feelings of fear, although the event was not objectively threatening (*i.e.* "I was living with my parents and my grandmother. I remembered being very much afraid of going to sleep in the evenings, because there was a Finnish rug hanging in the wall. The rug was displaying an owl, which looked very scary in the dim light"). We would need more cross-cultural data sets to explore whether differences in fear-related language use does exist and thus necessary to develop standards for each cultural/environmental setting. Either way, comparing these analyses across cultural settings by itself will be important and generate valuable data for fear-related mental health.

The above described approach and related analyses are based on the use of the same language in different cultures/environmental settings, allowing a cross-culture comparative approach. However, this might not always be feasible. For example, it would not be feasible to easily compare the use of fear-related language in a population using one language with that of another language, or a population using various dialects of the same language, such as British-English and American-English. The involvement of distinct translations and interpreters would add too much variability to allow for an easy cross-cultural comparison. An example of two distinct non-English languages would be studies of children living in the Gaza strip and Finland described above. Two

examples of native English-speaking cohorts in Australia are the Handy cohort of university students and a cohort of cancer survivors.

7. Interactions: are there relationships between fear learning and memory and other topic areas studied as part of the Human Affectome Project?

Fear learning and memory would be expected to affect most other topic areas studied as part of the Human Affectome Project. The topic areas especially expected to be affected are, in no particular order: (1) attention. Steady-state visually-evoked potentials for example have been used to demonstrate selective attention to specific imminent threat during fear (Kastner-Dom et al., 2018). Attention is also important for expectancy bias in fear (Aue and Okon-Singer, 2015); (2) happiness. Fear and happiness were shown to increases attentional flexibility (Storbeck et al., 2018); (3) hedonics. For example, fear learning affects psychological processes in chronic pain (Nees and Becker, 2017) and stress might contribute to pain-related fear in chronic pain (Eisenbruch and Wolf, 2015); (4) motivation. Emotions affects attention, and motivates actions and behaviors (Tyng et al., 2017); (5) physiological. Fear learning majorly affects physiology (Keifer et al., 2015); (6) planning; (7) sadness. Sadness was shown to facilitate the splitting of attention (Storbeck et al., 2018); (8) self. For example, increased perceived self-efficacy following verbal persuasion was shown to facilitate extinction of fear learning (Zlomuzica et al., 2015); and (9) social. Social fear learning, basically fear learning acquired through social transmission, is being studied in humans and animals (Debiec and Olsson, 2017).

8. Discussion

8.1. What is the degree of consensus in the area of fear learning and memory?

"Fear learning and memory" is typically studied using Pavlovian aversive conditioning procedures. The question of consensus in this area has to be addressed in terms of two sub-questions: (1) is there consensus about the definition of fear learning and memory? and (2) to what degree have empirical findings led to a consistent set of conclusions?

There is currently debate about what "fear" actually means. The standard position is that fear is a non-subjective brain state controlling hard-wired and learned behavioral responses to threats in addition to subjective experiences. The fearful brain state is often said to be amygdala-centered, as the amygdala is viewed as a hub of fear processing controlling behavior, physiology, and subjective experience. A second position is that fear is an innate subjective state, a feeling of being in harm's way. This state is also said to crucially involve the amygdala—danger induces fear in the amygdala, and the amygdala then controls behavioral and physiological responses. Those who ascribe to the first view often write and speak as though they ascribe to the second view, which has been a source of confusion. A third position also holds that fear is a subjective experience, but that it is cognitively assembled in the neocortex rather than an innate, programmed state programmed in the amygdala. In this view, the amygdala controls behavioral and physiological responses elicited by the threat rather than fear itself. These responses affect the state of fear, but are not one and the same.

The extent of empirical consensus has emerged as the result of behavioral and physiological responses; all three views generally agree that fear is controlled by the amygdala and related subcortical areas. However, inconsistencies arise when empirical findings are applied to clinical problems related to fear and anxiety. For example, efforts to find new pharmaceutical treatments have assumed subcortical-based views, often not distinguishing between the subjective and objective views of subcortical circuits, both of which assume that if there is a change in behavioral and physiological responses, then fearful experiences will also diminish. The third view predicts that specifically targeting subcortical areas to change behavioral and physiological responses will not necessarily change subjective feelings, as these are assembled by neocortical circuits. The failure of the drug discovery effort is more consistent with this third position, however there is still more investigation to be done to determine where and how fear learning and memory occurs and can be manipulated.

8.2. What are the gaps in knowledge in the area of fear learning and memory?

The largest gap in knowledge in this area of research involves the conscious experience of fear and its pathological manifestations. People with fear-related problems have a huge range of symptoms. They excessively avoid potentially fear-arousing situations, become hyper-vigilant and physiologically aroused when confronted with threats, and feel afraid often. Clearly, all of these symptoms need to be addressed. It is possible, given that the related neurocircuitry is somewhat distinct, that different symptoms might require different treatments. Pharmaceutical treatments arising from animal studies of behavioral and physiological responses are probably best suited for changing behavioral and physiological responses, but less suited to change human subjective experience. While these treatments may change the intensity of the experience, the cognitive structures that support a "fear state of mind" also needs to be changed, potentially requiring cognitive and mindfulness-based treatments targeted at feelings.

8.3. To what degree might the linguistic framework be valuable for basic and translational purposes for the area of fear learning and memory?

As described above, subjective experiences and autobiographies are valuable for analyzing fear and fear-related memories. Based on that, a linguistic framework is likely valuable for both basic and translation purposes. These analyses, for example, would be valuable for longitudinal analyses in individuals to track response to behavioral and/or pharmacological interventions and to assess fear and fear-related memories in individuals as part of challenging missions, such as deep space missions of astronauts.

8.4. Why is there a need in using and agreeing upon a common terminology for feelings and emotions related to fear learning and memory

For practical use of a linguistic approach within and across populations, it will be critical to use a common terminology for feelings and emotions related to fear learning and memory. Otherwise, it will be very hard to compare studies. A common terminology would also be critical for multi-site behavioral and pharmacological intervention studies for fear learning and memory disorders.

9. Conclusions: the need for an integrated model of affect that includes fear and other topic areas studied as part of the Human Affectome Project.

Once the details are worked out within one topic area, it would be worthwhile to integrate the model to include other topic areas studied as part of the Human Affectome Project that are likely related to the fear topic area, particularly those highlighted in Section 7.

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